A spherical molecular assembly formed by the interplay of hydrophobic and hydrogen bonding interactions. Formation of a hexameric ball

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ABSTRACT

A six-membered ball-like supramolecular structure of **1c** was obtained by the interplay of hydrophobic and hydrogen bonding interactions. Preferred H-bonding connectivity and the proximate side-chain groups in a hydrophobic core stabilized to form the ball structure as revealed by making a comparison with the linear tape structure in the crystal polymorph of **1c**.

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Nature makes use of noncovalent interactions to construct and manipulate diverse supramolecular assemblies, which reveal the particular importance of the interplay between hydrophobic and hydrogen bonding interactions. In folded proteins, the component amino acids create a backbone structure by hydrogen bonding, and their side chains are buried in the hydrophobic core to gain stability.[1,2] A particularly beautiful example is the leucine zipper protein, where the interdigitation of the isobutyl group of the leucine units facilitates the association between the proteins by hydrophobic interactions.[3] Actually, the interplay between these opposing forces is one of the fundamental factors controlling the structures of molecular assemblies and their stability, not only in biotic systems but also in abiotic systems, for example, α,ω-alkanediols and α,ω-alkanediamines, which show melting point alternation.[4] A variety of meticulously designed supramolecular aggregates have been reported.[5–7]

We have been attracted to the problem of manipulating hydrogen bonds for use in constructing supramolecular assemblies and have found 4-amino-6-oxopyrimidine **1a** and its derivatives (Fig. 1a).[8–10] This small molecule is packed with three H-bonding donor (D) atoms and two acceptor (A) atoms, one of which is a carbonyl oxygen having two directions of interactions (*syn* and *anti*).[11] We found that **1a** self-assembled to form stacks of the linear tape structure in the crystal form. The tape structure consists of the centrosymmetric H-bonded dimer, connected to each other by further complementary hydrogen bonds. A most revealing property of the aggregates of **1a** is their characteristic exciton band observed at 350 nm in the solution as well as in the crystal form, due to the merocyanine-type structure.[9] When one of the amino hydrogens was replaced by a methyl group (**1b**), the resultant crystals again contain stacks of linear tapes, though they are separated by walls

of two-dimensional water networks.[10] Thus, both **1a** and **1b** have a strong tendency to form linear tapes by H-bonding interactions between each molecule. Inspired by the leucine zipper protein,[3] we chose the isobutyl group as the substituent in **1c** to see if this side chain is enough to suppress the formation of the tapes. Here we report that the introduction of the isobutyl group changes the mode of self-assembly of **1c** to an extent more than we had anticipated. Namely, an interplay of hydrophobic and H-bonding interactions directs the molecule **1c** to form trimeric bowl assemblies, and the two bowls associate together to form an unprecedented hexameric ball-like supramolecular structure.

The compound **1c** was synthesized in three steps from 4,6-dichloropyrimidine (see the Supplementary data). The crystals of **1c** grown from water were found to contain a quarter molecule of water.[12] The crystal structure consisted of the tapes of **1c** connected to each other by the water molecules (Fig. 2). Alcohols, in which **1c** was highly soluble, gave polycrystals, as did common solvents. However, nitrobenzene, in which **1c** has only limited solubility at low temperatures, gave well-formed crystals. On close
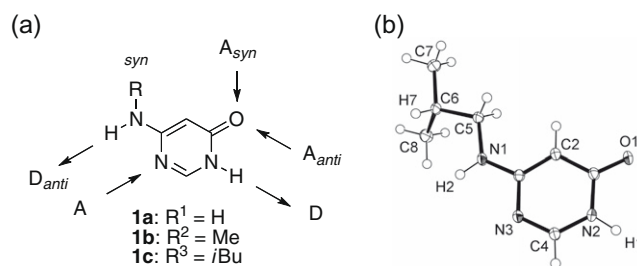
Figure 1. (a) Chemical structure of 4-amino-6-oxopyrimidines **1a–c**, showing schematic representation of the H-bonding sites. (b) The ORTEP drawing of **1c** (α crystals) with the selected numbering scheme.

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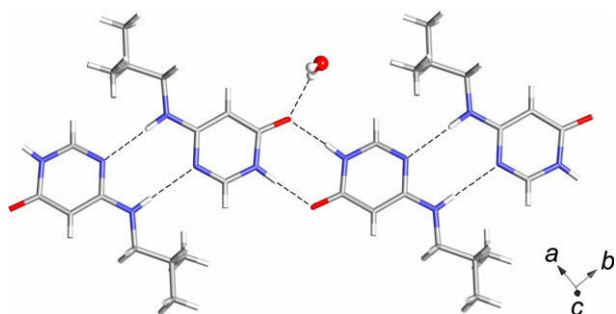
Figure 2. Perspective view of a linear tape arrangement of **1c** with a quarter molecule of water.

examination, there were two crystalline forms (Fig. S1). The separation of the crystals was quite easy, because the plate-like crystals (α form) sank to the bottom of the vessel, and the trapezoid crystals (β form) floated in nitrobenzene (d_{20} 1.203).[13]

The results of the X-ray crystallographic analysis of these two crystals are shown in Figure 3.[12] The α crystal contains one molecule in an asymmetric unit to form stacks of linear tapes as in the quarter-hydrated **1c** as well as in the crystals **1a** and **1b**. The molecule **1c** is paired with itself by the hydrogen bonds (N2···O1′ and N2′···O1 2.75 Å) to form a centrosymmetric dimer, which is further connected with the other dimer pairs by complementary hydrogen bonds (N1···N3″ and N1″···N3 3.10 Å). Therefore, the H-bonding connectivity motif of the molecules for the tape structure is the same as that for the crystals of **1a** to **1c**, even though the chemical structure and the degree of the participation of water molecules are considerably varied (Fig. S2).

In sharp contrast, the self-assembled structure of **1c** in the β crystals is remarkable (Fig. 3b). Three molecules of **1c** are present in an asymmetric unit and gathered together to make a distorted
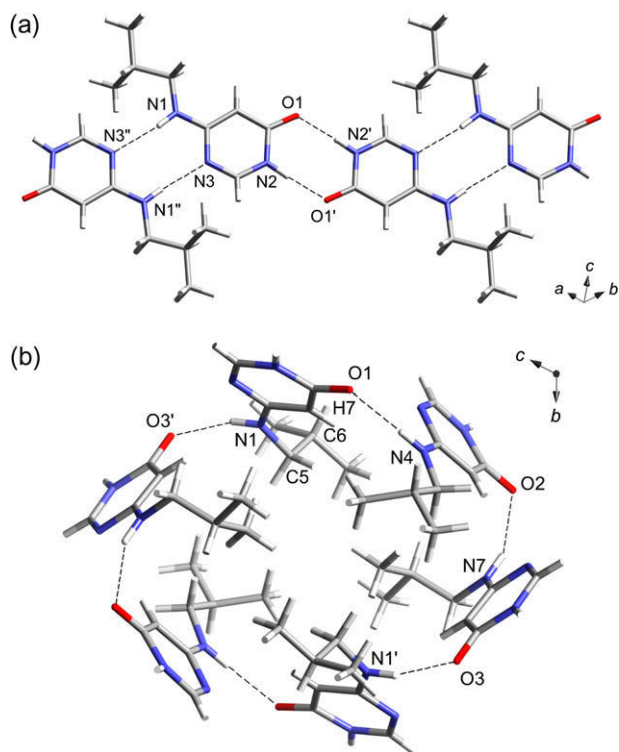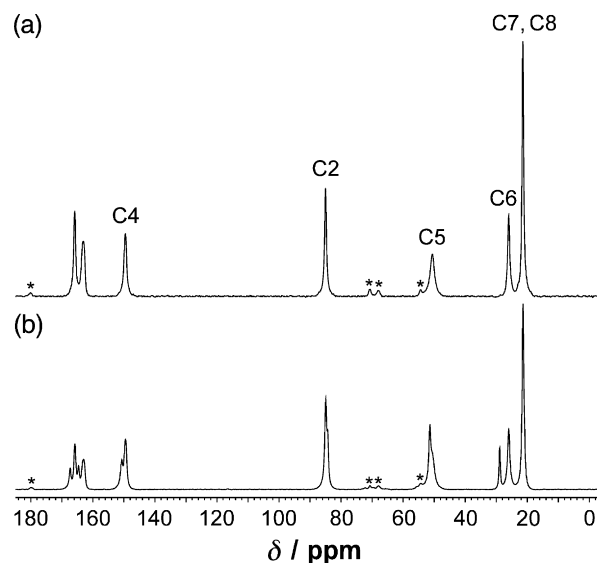
bowl structure. The bowl assembly is held together by the two hydrogen bonds (N4···O1 3.00 Å; N7···O2 2.93 Å). Then two of the bowls are fitted together in an alternate fashion through the two hydrogen bonds (N1···O3′ and N1′···O3 2.94 Å) to form a six-membered ball-like structure.

Of note, the H-bonding connectivity for the hexameric ball is considerably different from that found for the tape structure. In the tape structure, the H-bonding donor hydrogen at the isobutylamino group (N1–H2) is bound to the pyrimidine nitrogen (N3″), and the carbonyl oxygen (O1) accepts the donor hydrogen of the pyrimidine nitrogen (N2′) at its *anti* site (Fig. 3a). In the hexameric ball-like structure, on the other hand, the donor hydrogen atoms at the isobutylamino (N4, N7, and N1) groups are bound to the *syn* sites of the acceptor carbonyl oxygen atoms (O1, O2, and O3′, respectively) (Fig. 3b).

These differences in the H-bonding interactions between the tape and the spherical assemblies are reflected in the FT-IR spectrum. A rather sharp band attributable to the $\nu_{N1–H2}$ band for the isobutylamino group is shifted from 3257 cm^{-1} for the α crystals to 3251 cm^{-1} for the β crystals (Fig. S3). The shift of 6 cm^{-1} to the lower frequency indicates the increased strength of hydrogen bonding in the β crystals as compared to the α crystals in agreement with the superiority of the carbonyl oxygen over the pyrimidine nitrogen as a H-bonding acceptor.[14]

The direction and the arrangement of the hydrogen bonds in the six-membered spherical assembly appear to bring the hydrophobic side-chain groups into close contact. Two of the three molecules in the bowl are similar in their side-chain conformation, and their dihedral angles N1–C5–C6–H7 are (+) syn-clinal (53.9° and 56.1°), although one of them is (−) syn-clinal (− 55.2°). The isobutyl groups of the two molecules of **1c** constitute the rim of the bowl-like structure, and the remaining molecule of **1c** forms the bottom (Fig. S4).

The CPMAS ^{13}C NMR spectroscopy clearly demonstrates these structural properties (Fig. 4). While the number of the resonances for the α crystals corresponds to the one molecule in the asymmetric unit, the signals for the β crystals are split into two for most of the carbon in a ratio of 2:1, which is in agreement with the presence of the two configurations in a 2:1 ratio. Since the chemical shifts of the major peaks are very close to those of the peaks for the corresponding carbons of **1c** in the α crystals, the peaks for

Figure 3. Molecular arrangement of **1c** in crystals. (a) A one-dimensional tape via complementary hydrogen bonding (α crystals). (b) Six-membered spherical assembly of **1c** in the β crystals. Dashed lines represent the hydrogen bonding.

Figure 4. The CPMAS ^{13}C NMR spectra of the two crystal polymorphs of **1c**. (a) α crystals and (b) β crystals. The assignments correspond to the numbering scheme in Figure 1b. An asterisk denotes spinning sidebands.

the minor (−) syn-clinal molecule are shifted downfield, suggesting that its long range magnetic environment is significantly different from the other (+) syn-clinal molecules.

The results discussed so far are for the supramolecular structures in the crystalline state. Surprisingly, the trimeric and the six-membered assemblies are sustained in the solution, as evidenced by the electrospray ionization mass spectroscopy (Fig. S5). When an ethanolic solution of **1c** (1×10^{-4} M) was analyzed, a preponderant peak for the dimer ($[2M+Na]^+ = 357.25$, 100%) as well as the peaks for the trimer ($[3M+Na]^+ = 524.41$, 29.9%), tetramer ($[4M+Na]^+ = 691.56$, 29.4%), and hexamer ($[6M+Na]^+ = 1025.29$, 2.4%) were observed. Absence of the monomeric species was anticipated because of the tendency to form a pair, as observed in the crystals of **1a–c**. While the pentameric aggregate was absent, the hexameric cluster was observed even in dilute solution in the hydroxylic solvent, that is, under unfavorable conditions for self-assembly by H-bonding interactions.

Further support for the presence of the cluster molecules was provided by NMR diffusion measurements. NMR diffusion, as obtained from pulsed field gradient echo technique, is widely used for studying supramolecular assembly in organic solvents, and provides a diffusion coefficient (D). The diffusion-ordered NMR spectroscopy was performed for the methanolic solution of **1c** using 4,6-dichloropyrimidine as an external reference. The D of **1c** was decreased from 8.96×10^{-10} m^2 s^{-1} to 8.18×10^{-10} m^2 s^{-1} with increasing the concentration from 5×10^{-3} M to 0.10 M. The obtained D of both dilute and concentrated solutions of **1c** was significantly smaller than that of 4,6-dichloropyrimidine, which has little H-bonding interaction site (1.84×10^{-9} m^2 s^{-1}, 5×10^{-3} M). Since the ratio of the diffusion coefficients for the two different molecular species is subjected to be equal to the reciprocal of the cube root of the ratio of their molecular weight,[15] we could estimate the theoretical D for the molecule. The calculated D for **1c** was 1.78×10^{-9} m^2 s^{-1}, thus indicating that **1c** is clustered in solution.

More compelling evidence for the presence of the cluster molecules came from the ^{13}C NMR spectrum in MeOH-d_4 solution (Fig. 5). At ambient temperature, a solution of **1c** (0.10 M) showed broad resonances for all of the carbon, suggesting slow reorganization among the aggregates of **1c**. Upon cooling to 193 K, however, each of the resonances splits to two sets of peaks in an intensity ratio of 2:1, exactly corresponding to the peaks found for the β crystals. Accordingly, these observations indicated that the equilibrium of self-association of **1c** between the aggregates shifted to form the trimeric bowl assembly at lower temperature.

Transformation of the self-assembly of **1c** from the dimer in the tape to the trimer in the spherical assembly appears to be con-
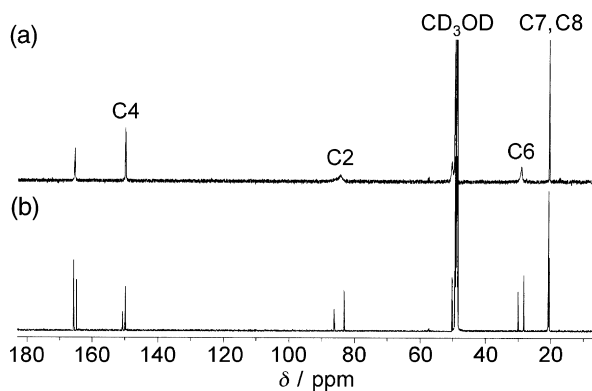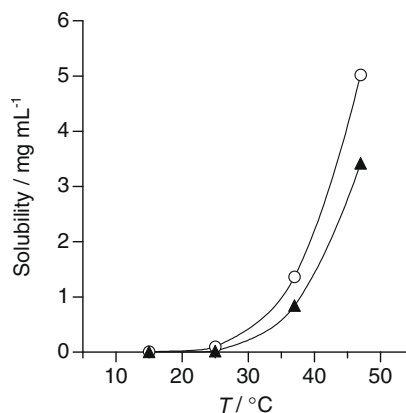
Figure 6. Solubility curves of the polymorphic crystals of **1c**. Open circles indicate the α crystals, and filled triangles correspond to the β crystals.

trolled by the balance of the two opposing forces: hydrophobic and hydrogen bonding interactions. Here a question arises as to why the molecule **1c** crystallized to the tape structure from polar water and to the spherical assembly from the less-polar nitrobenzene. In a view of the hydrophobic interactions, the reverse should be true. One explanation is as follows. In the solution, both the dimer and the trimer can exist to form cluster nuclei. However, in the process of forming bulk crystals, the solvent molecules play an important role. While hydrophobic interactions are likely to be effective in water, water molecules prevent the formation of the spherical assembly by bounding at the syn site of the carbonyl oxygen of **1c** (Fig. 2). To ascertain crystals grown from alcohols containing either the tape structure or the spherical assembly, the powder X-ray diffraction was performed. The diffraction of the crystals obtained from MeOH is almost in the same pattern as the α crystals (Fig. S6). Thus the local H-bonding interactions between **1c** and the protic solvents led to the tape structure in the crystals.

To gain information on the equilibrium of the self-assembly of **1c** between the solution and the crystalline phase, we determined the solubility of the α and β crystals over a temperature range of 15–47 °C. The results obtained are shown in Figure 6. At the temperature of 37 °C, the solubility of the α crystals is 1.6 times higher than that of the β crystals. Because solubility is related to the chemical potential between the solution and the crystalline phase,[16,17] the β crystals are in the stable form, while the α crystals are in the metastable form.

In summary, we have found that the simple isobutyl group can change the mode of the self-assembly of **1c** from the linear tape structure to the novel trimeric bowl and hexameric ball-like supramolecular structures. The six-membered spherical assembly is sustained by the preferred H-bonding connectivity and the side-chain groups in close contact. Of particular importance is the isolation of the two crystalline polymorphs, which makes comparative studies feasible in analyzing supramolecular structures of **1c** formed by the interplay of hydrophobic and H-bonding interactions, possibly with the deliberate use of the solvent.

Acknowledgments

Figure 5. The ^{13}C NMR spectrum in a 0.10 M MeOH-d_4 solution of **1c** at (a) ambient temperature and (b) 193 K. The assignments correspond to the numbering scheme in Figure 1b.

Supplementary data

Experimental details, characterizations, spectroscopic data, HPLC profiles, and crystallographic information are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.012.

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