

## Hydrogen-Bonding Control of Molecular Self-Assembly: Formation of a 2 + 2 Complex in Solution and the Solid State

Ji Yang, Erkang Fan, Steven J. Geib, and Andrew D. Hamilton\*

Materials Research Center and Department of Chemistry  
University of Pittsburgh, Pittsburgh, Pennsylvania 15260

Received December 28, 1992

Recently great strides have been made in the use of hydrogen bonding to control host-guest complexation<sup>1</sup> as well as crystal packing patterns.<sup>2,3</sup> However, there has been relatively little progress in the area between small molecules and polymers where three or more components are induced to form well-defined aggregates.<sup>4</sup> This intermediate molecular weight region ( $(1-20) \times 10^3$  Da) is of considerable importance in the development of nanometer-scale structures.<sup>5</sup> We have previously shown that the bidentate interaction between carboxylic acids and 2-acylamino-pyridines provides a strong and versatile binding motif for the formation of 1:1<sup>6</sup> or polymeric<sup>3</sup> hydrogen-bonded complexes, as in **1**. In this paper we demonstrate that cyclic 2 + 2 aggregates (as in Figure 1) can be formed in solution and in the solid state by diacid and bis-acylamino-pyridine subunits with appropriate spacers between the binding groups.

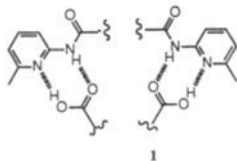
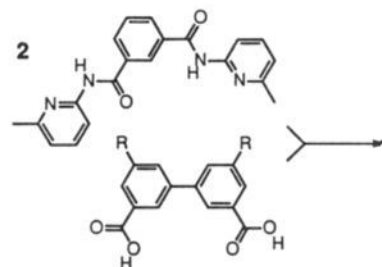
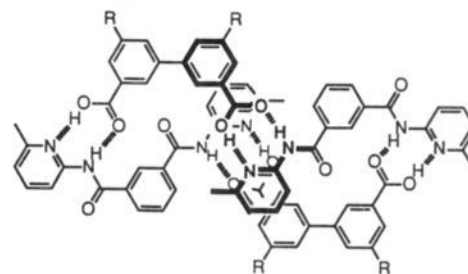
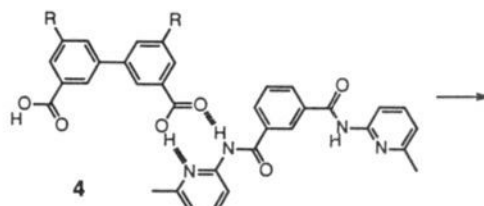


Figure 1.

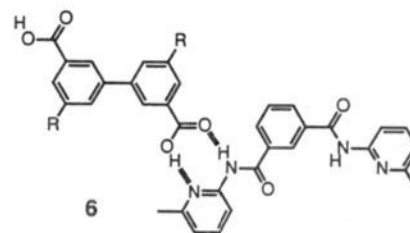
and aminopyridine sites point in the same direction, can further dimerize to 2 + 2 aggregate **5a**. In the 1:1 complex **6** between



**3a.** R=H. **3b.** R=CO<sub>2</sub>C<sub>10</sub>H<sub>21</sub>



**5a.** R=H. **5b.** R=CO<sub>2</sub>C<sub>10</sub>H<sub>21</sub>



Our approach to multicomponent complexes involved combining a small isophthaloyl receptor (**2**)<sup>6b</sup> with a diacid substrate that due to its size and conformational restrictions cannot form bidentate H-bonding interactions to both aminopyridine sites. Biphenyl-3,3'-dicarboxylic acid **3a**<sup>7</sup> is an interesting candidate for the diacid since it has two low-energy conformations, syn (as in **3a**) and anti, with markedly different dihedral angles between the phenyl rings.<sup>8</sup> A 1:1 interaction of the syn conformer with receptor **2** would lead to **4** which, because the free carboxylic acid

(1) For leading reviews, see: Diederich, F. N. *Cyclophanes*; Royal Society of Chemistry: London, 1991. Hamilton, A. D. In *Advances in Supramolecular Chemistry*; Gokel, G., Ed.; JAI Press: Greenwich, 1990; Vol. 1, p 1. Rebek, J., Jr. *Acc. Chem. Res.* **1990**, *23*, 399.

(2) For general references, see: Wright, J. D. *Molecular Crystals*; Cambridge University Press: Cambridge, 1987. Desiraju, G. D. *Crystal Engineering: The Design of Organic Solids*; Elsevier: New York, 1989. Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120. Zerkowski, J. A.; Seto, C.; Wierda, D. A.; Whitesides, G. M. *J. Am. Chem. Soc.* **1990**, *112*, 9025. Zhao, X.; Chang, Y. L.; Fowler, F. W.; Lauher, J. W. *J. Am. Chem. Soc.* **1990**, *112*, 6627. Simard, M.; Su, D.; Wuest, J. D. *J. Am. Chem. Soc.* **1991**, *113*, 4697. Lehn, J. M.; Mascal, M.; DeCian, A.; Fisher, J. J. *Chem. Soc., Perkin Trans. 2* **1992**, 461.

(3) Garcia-Tellado, F.; Geib, S. J.; Goswami, S.; Hamilton, A. D. *J. Am. Chem. Soc.* **1991**, *113*, 9265. Geib, S. J.; Vicent, C.; Fan, E.; Hamilton, A. D. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 119.

(4) For notable exceptions, see: Seto, C. T.; Whitesides, G. M. *J. Am. Chem. Soc.* **1990**, *112*, 6409. Seto, C. T.; Whitesides, G. M. *J. Am. Chem. Soc.* **1991**, *113*, 712. Zimmerman, S. C.; Duerr, B. F. *J. Org. Chem.* **1992**, *57*, 2215.

(5) For recent reviews on self-assembly, see: (a) Lindsey, J. S. *New J. Chem.* **1991**, *15*, 153. (b) Whitesides, G. M.; Mathias, J. P.; Seto, C. T. *Science (Washington, D.C.)* **1992**, *254*, 1312.

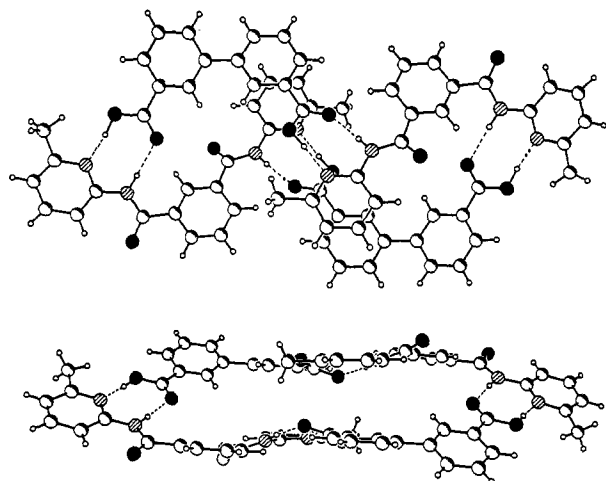
(6) For example: (a) Garcia-Tellado, F.; Goswami, S.; Chang, S. K.; Geib, S.; Hamilton, A. D. *J. Am. Chem. Soc.* **1990**, *112*, 7393. (b) Hirst, S. C.; Hamilton, A. D. *J. Am. Chem. Soc.* **1991**, *113*, 382. (c) Vicent, C.; Hirst, S. C.; Tellado, F.; Hamilton, A. D. *J. Am. Chem. Soc.* **1991**, *113*, 5466.

(7) Synthesized by oxidation (KMnO<sub>4</sub>) of 3,3'-dimethylbiphenyl.

(8) Estimated at ~40° for the syn and ~140° for the anti, using MacroModel (Still, C. Columbia University).

the anti conformer of biphenyl-3,3'-dicarboxylic acid and **2**, the free hydrogen-bonding sites are disposed in different directions and only polymeric aggregates, as seen with aliphatic diacids,<sup>3</sup> can form. Crystallization of an equimolar mixture of **2** and biphenyl-3,3'-dicarboxylic acid from a THF/hexanes solution confirmed the formation of a 2 + 2 aggregate in the solid state. Figure 2 shows the X-ray structure<sup>9</sup> of the complex, which takes up a cyclic arrangement of alternating diacid-diamide units linked

(9) Crystal data for C<sub>34</sub>H<sub>28</sub>N<sub>4</sub>O<sub>6</sub>: triclinic, *P* $\bar{1}$ , *a* = 9.201(2), *b* = 11.250(2), and *c* = 14.638(3) Å,  $\alpha$  = 73.71(3)°,  $\beta$  = 81.20(3)°,  $\gamma$  = 86.09(3)°, *V* = 1436.9(5) Å<sup>3</sup>, *Z* = 2, *d*<sub>calcd</sub> = 1.360 g cm<sup>-3</sup>, at 296 K. A Rigaku AFC5R diffractometer was used to collect 4730 data points, of which 3076 data with (*F* > 5.0σ > (*F*)) were used in the solution and refinement. X-ray data were corrected for absorption (*I*(Cu Kα) = 1.54178 Å). Structure was solved by direct methods which located all non-hydrogen atoms. Hydrogen atom positions were calculated (*d*(C-H) = 0.96 Å), except for N-H and O-H hydrogens which were located and refined. Structure refined to *R*(*F*) = 5.39% and *R*<sub>w</sub>(*F*) = 8.35%; *GOF* = 1.47; highest final difference peak, 0.27 e/Å<sup>3</sup>.



**Figure 2.** Top and side views of the X-ray structure of the complex formed between **2** and **3a**.

by eight hydrogen bonds (N...O distances, 2.70–2.93 Å), leading to an angle between the vectors of each carboxylic acid of 67°. The overall shape is a figure-of-eight with the outwardly directed aminopyridine–carboxylic acid region stacking at a distance of ~3.5 Å to the corresponding region on the opposite side of the macrocycle. The 2 + 2 aggregate resides on a crystallographic inversion center, and no hydrogen bonds are formed between adjacent aggregates, underlining their integrity.

The persistence of the 2 + 2 complex in solution was studied by NMR, gel permeation chromatography, and vapor-phase osmometry, using the more soluble biphenyl diacid **3b**.<sup>10</sup> The <sup>1</sup>H NMR spectrum of an equimolar mixture of **2** and **3b** (each at 10 mM) in CDCl<sub>3</sub> at 25 °C shows, in addition to the downfield shifts of the amide-H resonance due to hydrogen bonding, upfield shifts of the pyridine–CH<sub>3</sub> and –5H resonances (0.5 and 0.3 ppm), compared to the uncomplexed subunits. Such shifts are consistent with a complex of structure **5b** in which one of the two pyridine rings in **2** is positioned above the benzoic acid subunit.<sup>11</sup>

Gel permeation chromatography has been used effectively to assess both the size and the stability of aggregated structures.<sup>12</sup> The individual components **3b** (MW = 611) and **2** (MW = 346) show sharp peaks with long retention times (21.0 and 20.4 min; Figures 3A and 3B), while an equimolar mixture of **2** and **3b** (at 30 mM) gives a peak with a shorter retention time (17.6 min; Figure 3C), as expected for a larger aggregate.<sup>13</sup> The sharpness of this peak indicates the formation of a well-defined structure in solution with some dissociation of the aggregate on the column, as evidenced by the tailing visible in Figure 3C. The molecular weight of the aggregate was estimated, by comparison to a series of standards, to be 1970 ± 100, which is close to that calculated for the 2 + 2 aggregate **5b** (MW = 1914). Figure 3D shows as an example the chromatogram of a similarly-sized triple-decker porphyrin (MW = 1704).<sup>14</sup>

Vapor-phase osmometry studies at 25 °C in CH<sub>2</sub>Cl<sub>2</sub> over the concentration range 16–50 mM gave an apparent molecular

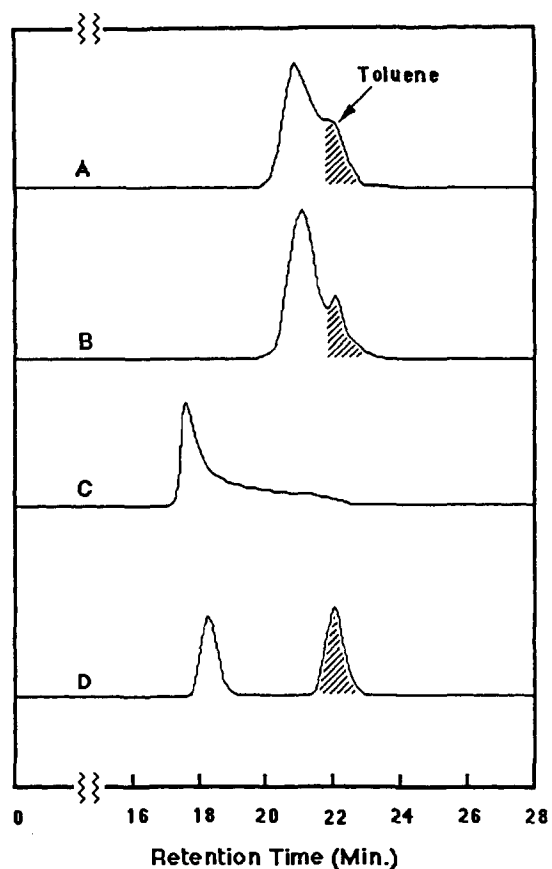
(10) Formed by coupling benzyldodecyl 5-iodoisophthalate with Ni(TPP)<sub>3</sub> followed by hydrogenation. Kende, A. S.; Liebeskind, L. S.; Braitsch, D. M. *Tetrahedron Lett.* **1975**, 3375.

(11) Under these conditions the complex is in fast exchange with no differentiation of the two pyridine regions.

(12) Seto, C. T.; Whitesides, G. M. *J. Am. Chem. Soc.* **1993**, *115*, 1321.

(13) Run on a Waters Ultrastaygel 10<sup>3</sup>-Å GPC column with CH<sub>2</sub>Cl<sub>2</sub> as eluent at a flow rate of 0.5 mL min<sup>-1</sup>.

(14) Chosen due to its similar size and chemical makeup. Dubowchik, G.; Hamilton, A. D. *J. Chem. Soc., Chem. Commun.* **1986**, 665.



**Figure 3.** Gel permeation chromatograms with CH<sub>2</sub>Cl<sub>2</sub> as eluent and toluene as standard for: A, **3b** (3 mM); B, **2** (30 mM); C, **2:3b** (1:1, 30 mM); and D, triple porphyrin<sup>14</sup> (0.1 mM).<sup>13,15</sup>

weight for the aggregate of 1400 ± 100. This value is lower than that expected for the 2 + 2 complex and presumably reflects the presence of some smaller aggregates in the equilibrium mixture. Analysis of the data according to the method of Schrier<sup>16</sup> allows the aggregation equilibria to be taken into account and shows that >80% of the species in solution (at 16–50 mM) is the 2 + 2 complex.

In summary, we have shown that two subunits of appropriate design can be induced to form, both in solution and in the solid state, discrete 2 + 2 aggregates stabilized by a network of hydrogen bonds. This strategy provides an important entry into the design of self-assembling structures with photoactive and redox-active components.

**Acknowledgment.** We thank the National Science Foundation (CHE 9213937) and the AFOSR (University of Pittsburgh, Materials Research Center) for support of this work. We also thank Prof. George Whitesides for helpful suggestions.

**Supplementary Material Available:** Crystallographic details for 2 + 2 aggregate **5a** (Figure 2) including tables of atomic coordinates, thermal parameters, bond angles, and bond lengths (10 pages); listing of observed and calculated structure factors (17 pages). Ordering information is given on any current masthead page.

(15) For Figures 3A, B, and D, detection was carried out at 250 nm, and for Figure 3C detection was at 320 nm.

(16) Schrier, E. E. *J. Chem. Educ.* **1968**, *45*, 176. For a more recent example, see: Beak, P.; Covington, J. B.; Smith, S. G.; White, J. M.; Zeigler, J. M. *J. Org. Chem.* **1980**, *45*, 1354.