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Preorganizing Linear (Self-Complementary) Quadruple Hydrogen-Bonding Arrays Using Intramolecular Hydrogen Bonding as the Sole Force

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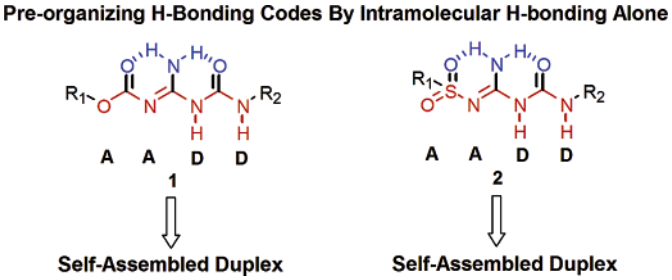

In this article we describe a rational approach for prefixing multiple cooperative binding sites in an ideal spatial arrangement on a structurally rigid backbone, constrained *exclusively* by intramolecular hydrogen bonding. The idea is exemplified by the ability of the self-assembling constructs **1a**−**e** and **2a**,**b** to form hydrogen-bonded dimers, whose structural preorganization has been solely effected by intramolecular hydrogen bonding. The readily accessible amidinourea backbone has been used as a common platform for the construction of a variety of such self-assembling systems. ESI mass spectrometry and single-crystal X-ray diffraction studies have been particularly effective in investigating the self-assembling propensities of these systems. Remarkably, most the H-bonded dimers reported herein undergo an unusual mode of self-assembly, using intermolecular four-membered ring hydrogen-bonded interaction, affording extended supramolecular networks.

Introduction

Over the past three decades, chemists have made key strides in learning the fundamental rules of self-assembling processes involving noncovalent interactions, in particular hydrogen bonding.[1,2] Owing to the directionality and specificity,[3,4] hydrogen bonds are particularly useful for the programmed self-assembly of smaller molecular components to generate supramolecular ensembles with predefined structural features. Hydrogen bond-mediated self-assembly is achieved mainly by preorganizing the acceptor (A) and donor (D) hydrogen-bonding codes in a desired fashion.[5,6] Preorganization of the hydrogen-bonding codes also has a direct influence on the stability of the self-assembled ensembles.[7] A perusal of the structures of many such programmed self-assembling systems reported in the literature (Figure 1) reveals that covalent linkages, in combination with intramolecular hydrogen bonding, have been invariably used to preorganize the hydrogen-bonding codes, and these covalent linkages usually form part of the hetero-

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(1) (a) Lehn, J.-M. *Supramolecular Chemistry: Concepts and Perspectives*; VCH: Weinheim, Germany, 1995. (b) Steed, J. W.; Atwood, J. L. *Supramolecular Chemistry*; Wiley: New York, 2000. (c) Whitesides, G. M.; Grzybowski, B. *Science* **2002**, *295*, 2418−2421. (d) Whitesides, G. M.; Mathias, J. P.; Seto, C. T. *Science* **1991**, *254*, 1312−1319. (e) Lehn, J.-M. *Polym. Int.* **2002**, *51*, 825−839. (f) Prins, L. J.; Reinhoudt, D. N.; Timmerman, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 2383−2426. (g) Bushey, M. L.; Nguyen, T.-Q.; Zhang, W.; Horoszewski, D.; Nuckolls, C. *Angew. Chem., Int. Ed*. **2004**, *43*, 5446−5453. (h) Conn, M. M.; Rebek, J., Jr. *Chem. Rev*. **1997**, *97*, 1647−1668. (i) Lindsey, J. S. *New J. Chem*. **1991**, *15*, 153−180. (j) Fredericks, J. R.; Hamilton, A. D. *In Comprehensive Supramolecular Chemistry*; Atwood, J. L., Ed.; Pergamon: New York, 1996; Vol. 9, pp 565−594. (k) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893−4011. (l) Sessler, J. L.; Jayawickramarajah, J. *Chem. Commun*. **2005**, 1939−1949. (m) Archer, E. A.; Gong, H.; Krische, M. J. *Tetrahedron* **2001**, *57*, 1139−1159. (n) Yagai, S.; Karatsu, T.; Kitamura, A. *Chem.−Eur. J.* **2005**, *11*, 4054−4063. (o) Sessler, J. L.; Jayawickramarajah, J. *Chem. Commun*. **2005**, 1939−1949.

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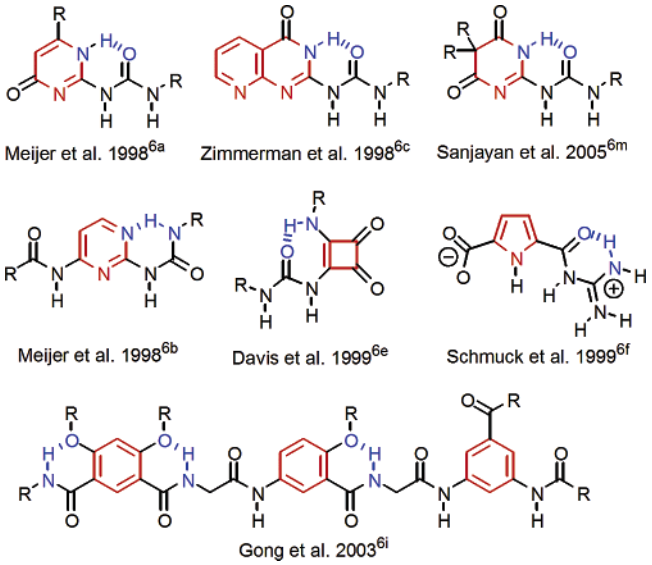

FIGURE 1. Selected examples of preorganized self-complementary self-assembling modules that form H-bonded dimers. For ease of identification, covalent bonds and intramolecular hydrogen bonds involved in preorganization of the hydrogen-bonding codes are colored red and blue, respectively.

cyclic ring on which the hydrogen-bonding codes are appended.[5,6]

Design Principles. In an effort to explore the potential of using intramolecular hydrogen bonding as the sole driving force in preorganizing linear hydrogen-bonding arrays, we generated a series of self-assembling modules whose linear quadruple hydrogen-bonding arrays were embedded on an acyclic amidinourea framework (Figure 2). It was anticipated that the primary amino group in **1** and **2** would hold the hydrogen-bonding codes (**A** and **D**) in a preorganized manner due to the possibility of formation of two intramolecular hydrogen-bonding interactions, as depicted in Figure 2. Structural studies (vide infra) indeed showed that such an arrangement of the linear hydrogen-bonding array on the amidinourea framework indeed favored the preorganization of the hydrogen-bonding codes, under the influence of two intramolecular hydrogen bondings. The strategy disclosed herein has the potential for significantly augmenting the "tool box" of the modern day supramolecular chemist, as well as providing a novel approach in the rational design of molecular recognition systems using the concept of intramolecular hydrogen bonding as the sole driving force for preorganization.[8]

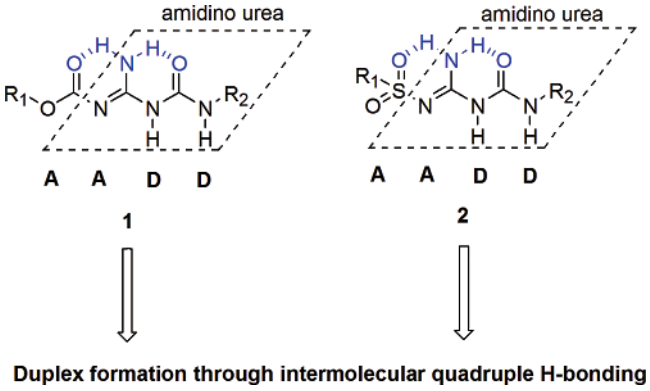

FIGURE 2. Amidinourea-based self-complementary self-assembling modules with preorganized linear hydrogen-bonding arrays. Intramolecular hydrogen-bonding sites that prefix the linear hydrogen-bonding codes have been highlighted in blue.

Results and Discussion

The self-assembling modules **1** and **2** are quickly accessible in good yield from the readily available bisboc guanidine[9] **3**, which served as a common synthon for both **1** and **2** (Scheme 1). The carbamate-protected amidinoureas **1a**,**c**,**d**,**e** could be easily synthesized by reacting the *N*,*N*′-di-boc-guanidine **3** with various amines under reflux condition in THF. It is noteworthy that the urea formation in this reaction is achieved by the reaction of amines (R_2NH_2) with the in situ generated isocyanate

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(5) For excellent recent reviews, see: (a) Brunsveld, L.; Folmer, B. J. B.; Meijer, E. W.; Sijbesma, R. P. *Chem. Rev.* **2001**, *101*, 4071−4097. (b) Sijbesma, R. P.; Meijer, E. W. *Chem. Commun.* **2003**, 5−16. (c) Zimmerman, S. C.; Corbin, P. S. *Struct. Bonding (Berlin)* **2000**, *96*, 63−94. (d) Schmuck, C.; Wienand, W. *Angew. Chem., Int. Ed.* **2001**, *40*, 4363−4369.

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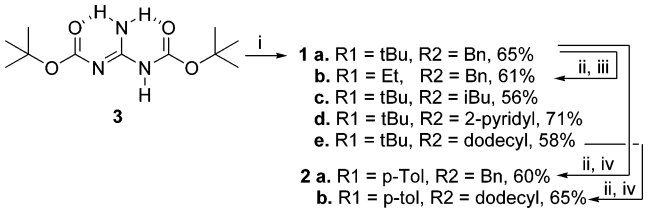
(8) The importance of the preorganization of binding sites in host−guest complexation processes has long been recognized. See, for example: (a) Cram, D. J. *Angew. Chem., Int. Ed.* **1988**, *27*, 1009−1020. (b) Gerbeleu, N. V.; Arion, V. B.; Burgess, J. *Template Synthesis of Macrocyclic Compounds*; Wiley-VCH: Weinheim, Germany, 1999. (c) *Templated Organic Synthesis*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 2000. (d) Gatti, F. G.; Leigh, D. A.; Nepogodiev, S. A.; Slawin, A. M. Z.; Teat, S. J.; Wong, J. K. Y. *J. Am. Chem. Soc.* **2001**, *123*, 5983−5989.

(9) Feichtinger, K.; Zapf, C. S.; Heather, L.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 3804−3805.

SCHEME 1. Synthesis of 1 and 2[a]



[a] Reagents and conditions: (i) R_2NH_2, THF, reflux, 12 h. (ii) TFA/DCM (1:1, v/v), 30 min. (iii) $ClCO_2Et$, Et_3N, DCM, 12 h. (iv) *p*-Tos-Cl, Et_3N, DCM, 12 h.

from **3**.[10] The *N*-ethyl carbamate analogue **1b** could be readily obtained in two steps from **1a** by first deblocking its ^{t}Boc group by short exposure to TFA/DCM (1:1, v/v) followed by reaction with ethyl chloroformate. The sulfonylated amidinoureas **2a**,**b** were synthesized by tosylation of the free amidinoureas, obtained from **1a**,**e**, respectively, by deprotecting their ^{t}Boc group by short exposure to TFA/DCM (1:1, v/v).

Self-assembling modules **1** and **2** were readily soluble in nonpolar solvents such as $CDCl_3$, which suggested that the NH protons were solvent shielded.[11] However, detailed solution-state NMR studies, including the determination of stability constants, could not be undertaken due to the existence of multiple conformations,[12] as evidenced by the broad proton resonances. Nevertheless, the formation of discrete dimers **1.1** and **2.2** was confirmed by ESI mass spectrometry.[13] In addition to the molecular ion peaks (MH^+) that are due to the monomers **1** and **2**, the ESI spectra (see Supporting Information) showed sizable peaks corresponding to the dimers **1.1** (M_2H^+) and **2.2** (M_2H^+).

Presumably due to their efficient packing in crystal lattices, the self-assembling modules **1a**−**d** and **2a**,**b** readily crystallized under ambient conditions.[14] To gain more insights into the self-assembling propensities of these self-assembling modules, a detailed crystal structure study of a diverse set of differentially substituted analogues was undertaken.[15] Comparison of the crystal structures of **1a**−**d** and **2a**,**b** revealed the following facts. All of the self-assembling constructs **1** and **2**, irrespective of the nature of substituents, underwent dimer formation through intermolecular hydrogen bonding, although a substantial difference existed in the mode of their assembly. In all but one case (**1c**, see vide infra), the *programmed* double intramolecular hydrogen bonding, characterized by the graph set S(6),[16] was indeed proved to be effective in preorganizing the self-complementary AADD-type hydrogen-bonding codes for duplex formation. Although all of these self-assembling modules **1** and **2** were expected to dimerize through quadruple hydrogen bonding due to their similar AADD-type hydrogen-bonding codes, the results of crystal structure investigations revealed substantial deviations from this conjecture. It was observed that, in general, substituents exerted a profound role in dictating the mode of hydrogen bonding in the duplex formation, **1.1** and **2.2**, (Figure 3). It is noteworthy that similar observations have been reported in heterocycle-based AADD-type quadruple hydrogen-bonding self-assembling systems.[17]

The key role of substituents in influencing the mode of hydrogen bonding in duplex formation is clearly evident in the comparison of crystal structures of **1a**−**d**. Whereas the closely resembling analogues **1a** and **1b**, which differ only in their carbamate substituents, show the same trend in the duplex formation (**1.1a** and **1.1b**) through quadruple AADD-type intermolecular hydrogen bonding, as expected, the *N*-isobutyl-substituted analogue **1c** formed duplex **1.1c** through N−H···N-type intermolecular double hydrogen-bonded interaction. The nonformation of a *quadruply* hydrogen-bonded duplex **1.1c** is presumably due to the crystal-packing forces that may be influencing the adopted conformations and orientations. The intermolecular hydrogen-bonding interactions (graph set C(4))[16] in the dimers **1a**−**d** are of medium strength[3] since the hydrogen bonding D−H···A distances (d(N−H···X); where X = N or O) are in the range 2.09−2.67 Å. However, the (S-6)-type intramolecular hydrogen bondings in the series **1a**−**d** remained relatively stronger[3] (d(N···O_{avg}) = 2.01 Å).

In an effort to investigate the influence of an additional acceptor atom on the N-substituent in modulating the hydrogen-bonding codes in duplex formation, **1d** was synthesized. It was observed that, having a 2-pyridyl N-substituent,[19] **1d** formed ADAD-type quadruple hydrogen-bonded duplex, a mode of hydrogen bonding that is in stark contrast to what is observed in **1a**−**c**. The strong bias toward the ADAD-type intermolecular hydrogen bonding involving pyridine nitrogen could be due to its better H-bonding acceptor potential when compared to the ether oxygen of the carbamoyl moiety.[16,20] It is noteworthy that heterocycle-based ADAD-type self-assembling motifs whose linear hydrogen-bonding arrays were preorganized by a combination of covalent linking

(10) Miel, H.; Rault, S. *Tetrahedron Lett*. **1998**, *39*, 1565−1568.

(11) Compounds having solvent-exposed acidic protons usually show poor solubility in organic solvents due to the aggregation phenomenon. See, for instance: (a) Mathias, J. P.; Simanek, E. E.; Whitesides, G. M. *J. Am. Chem. Soc.* **1994**, *116*, 4326−4340. (b) Damodaran, K.; Sanjayan, G. J.; Rajamohanan, P. R.; Ganapathy, S.; Ganesh, K. N. *Org. Lett*. **2001**, *3*, 1921−1924.

(12) Wilcox, C. S. In *Frontiers in Supramolecular Chemistry and Photochemistry*; Schneider, H. J., Durr, H., Eds.; VCH: Weinheim, Germany, 1990; pp 123−144.

(13) ESI mass spectrometry is an effective tool in investigating the formation of hydrogen-bonded molecular dimers. See, for instance, ref 6.

(14) Hydrogen-bonded self-assembling systems usually show poor tendency to crystallize under ordinary conditions, presumably due to their inefficient packing in crystalline lattices. See: *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vogtle, F., Eds.; Pergamon Press: Oxford, 1996; Vol. 9, pp 671−700.

(15) The crystal structure of **1a**,**b**,**d**,**e** and **2a**,**b** were solved by direct method using SHELXS-97, and the refinement was performed by full matrix least squares of F^2 using SHELXL-97 (Sheldrick, G. M. *SHELX-97: Program for Crystal Structure Solution and Refinement*; University of Göttingen: Göttingen, Germany, 1997). Hydrogen atoms were included in the refinement as per the riding model. CIF files are available in the Supporting Information.

(16) For the application of graph notation to hydrogen-bonding motifs, see: Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120−126.

(17) This is not surprising, given the fact that even highly stable molecular dimers are shown to be sensitive to the steric and electronic environments. See ref 6a,m.

(18) These figures were generated using PyMOL molecular graphics system. DeLano, W. L. *The PyMOL Molecular Graphics System*. http://www.pymol.org, 2004.

(19) 2-Amino pyridine motif (self-complementary AD-type) has been used for the construction of self-assembled H-bonded molecular ensembles. See: (a) Gong, H.; Krische, M. J. *J. Am. Chem. Soc*. **2005**, *127*, 1719−1725. (b) Leung, M. K.; Mandal, A. B.; Wang, C. C.; Lee, G. H.; Peng, S. M.; Cheng, H. L.; Her, G. R.; Chao, I.; Lu, H. F.; Sun, Y. C.; Shiao, M. Y.; Chou, P. T. *J. Am. Chem. Soc*. **2002**, *124*, 4287−4297.

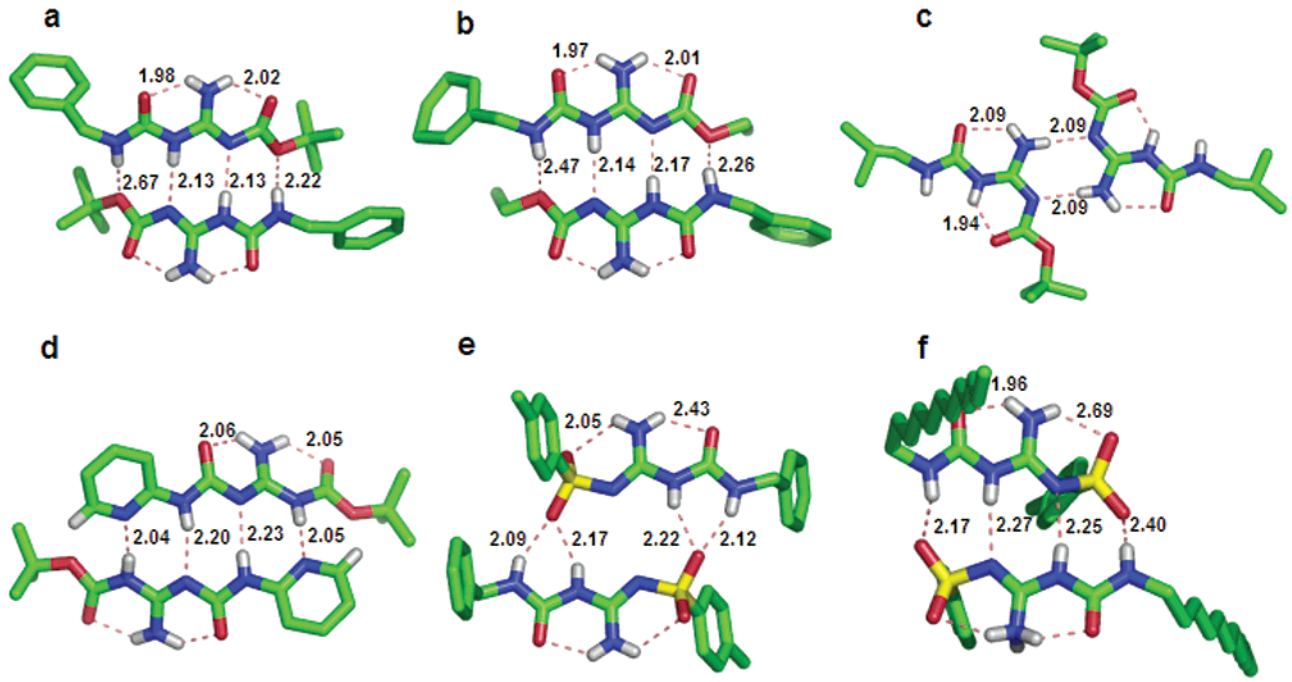


FIGURE 3. Single-crystal X-ray structures of dimers a (**1.1a**), b (**1.1b**), c (**1.1c**), d (**1.1d**), e (**2.2a**), and f (**2.2b**). Hydrogen bonding is highlighted in dashes (salmon colored), above which hydrogen bond distances (N−H···N and N−H···O) are displayed in Å. All hydrogens, other than those at the hydrogen-bonding sites, have been deleted for clarity. This figure was made using PyMOL.[18]

and intramolecular H-bonding have been reported in the literature.[6b,l]

An interesting feature of the self-assembling constructs **1a**−**c** is the deployment of both carbamoyl oxygens (carbonyl and ether oxygens) in hydrogen-bonding interactions, a situation that is not commonly observed in self-assembling systems.[5,6] In the self-assembling constructs **1a**−**c**, the carbamoyl carbonyl oxygen atoms have been found to be involved in intramolecular hydrogen bonding, thereby preorganizing the linear array of hydrogen-bonding codes, while the ether oxygen atom (of the carbamoyl moiety) takes part in self-assembly through intermolecular hydrogen-bonding interactions. However, the contribution of the intermolecularly hydrogen-bonding ether oxygen atom (of the carbamoyl moiety) toward the stability of the dimers and self-assembled ensembles would be minimal due to its reduced hydrogen-bonding acceptor potential.[20] Indeed, extensive studies[20a] have revealed that ester and lactone oxygens (both sp3 and sp2 oxygen atoms) are very poor hydrogen-bonding acceptors due to their the reduced hydrogen-bonding acceptor potential, which in turn is due to their reduced Brønsted basicity.[20a,21]

Sulfonamides have been used as flexible and polar peptidomimetic isosteres of carboxamides.[22] Further interest in this class of carboxamide isosteres stems from the fact that the more acidic N−H of sulfonamides may give rise to stronger hydrogen bonds.[23] To evaluate the potential of sulfonamides in hydrogen bond-mediated duplex formation, **2a**,**b** were synthesized. Analysis of the crystal structures revealed that hydrogen bond-mediated dimer formation was indeed realized, independent of the nature of the substituents, although the mode of hydrogen bonding was significantly affected, as in the case of **1a**−**d**. Whereas **2b**, having a dodecyl urea N-substituent, formed duplex through AADD-type quadruple hydrogen bonding, as expected, the analogous benzyl-substituted **2a** failed to dimerize in a similar manner, presumably due to the crystal-packing forces that may be influencing the adopted conformations and orientations. Instead, **2a** underwent dimerization through urea-type hydrogen bonding,[24,25] with the graph set C(4) [$R^1_2(6)$].[16]

(20) (a) Kelly, T. R.; Kim, M. H. *J. Am. Chem. Soc*. **1994**, *116*, 7072−7080. (b) Smith, P. J.; Reddington, M. V.; Wilcox, C. S. *Tetrahedron Lett.* **1992**, *33*, 6085.

(21) (a) Sutherland, I. O. In *Comprehensive Organic Chemistry*; Barton, D., Ollis, W. D., Eds.; Pergamon: Oxford, 1979; Vol. 2, p 869. (b) Fischer, A.; Mann, B. R.; Vaughan, J. *J. Chem. Soc*. **1961**, 1093. (c) Jaffe, H. H.; Freed, L. D.; Doak, G. O. *J. Am. Chem. Soc.* **1953**, *75*, 2209. (d) Chanley, J. D.; Feagewn, E. *J. Am. Chem. Soc.* **1955**, *77*, 4002. (e) Cerfontain, H.; Telder, A. K.; Kruk, G. C. *Tetrahedron Lett.* **1975**, 3639. (f) Amett, E. M. *Prog. Org. Chem.* **1963**, *1*, 223.

(22) For selected examples, see: (a) Gude, M.; Piarulli, U.; Potenza, D.; Salom, B.; Gennari, C. *Tetrahedron Lett.* **1996**, *37*, 8589−8592. (b) Gennari, C.; Nestler, H. P.; Salom, B.; Still, W. C. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 1765−1768.

(23) Moree, W. J.; van der Marel, G. A.; Liskamp, R. J. *J. Org. Chem*. **1995**, *60*, 5157−5169

(24) (a) Moreau, J. J. E.; Vellutini, L.; Man, M. W. C.; Bied, C.; Dieudonn, P.; Bantignies, J. L.; Sauvajol, J. L. *Chem.−Eur. J*. **2005**, *11*, 1527−1537. (b) Varghese, R.; George, S. J.; Ajayaghosh. A. *Chem. Commun*. **2005**, 593−595.

(25) Due to their highly directional hydrogen-bonding interactions, urea-based self-complementary systems have been extensively used for the generation of a myriad of self-assembling systems and organogelators. See: (a) van Esch, J. H.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2000**, *39*, 2263−2266. (b) Schoonbeek, F. S.; van Esch, J. H.; Wegewijs, B.; Rep, D. B. A.; de Haas, M. P.; Klapwijk, T. M.; Kellogg, R. M.; Feringa, B. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 1393−1397. (c) Schoonbeek, F. S.; van Esch, J. H.; Hulst, R.; Kellogg, R. M.; Feringa, B. L. *Chem.−Eur. J*. **2000**, *6*, 2633−2643. (d) Shirakawa, M.; Kawano, S.-i.; Fujita, N.; Sada, K.; Shinkai, S. *J. Org. Chem.* **2003**, *68*, 5037−5044. (e) Dulic, D.; van der Molen, S. J.; Kudernac, T.; Jonkman, H. T.; de Jong, J. J. D.; Bowden, T. N.; van Esch, J.; Feringa, B. L.; van Wees, B. J. *Phys. Rev. Lett*. **2003**, *91*, 207402−207405. (f) De Jong, J. J. D.; Lucas, L. N.; Kellogg, R. M.; van Esch, J. H.; Feringa, B. L. *Science* **2004**, *304*, 278−281.

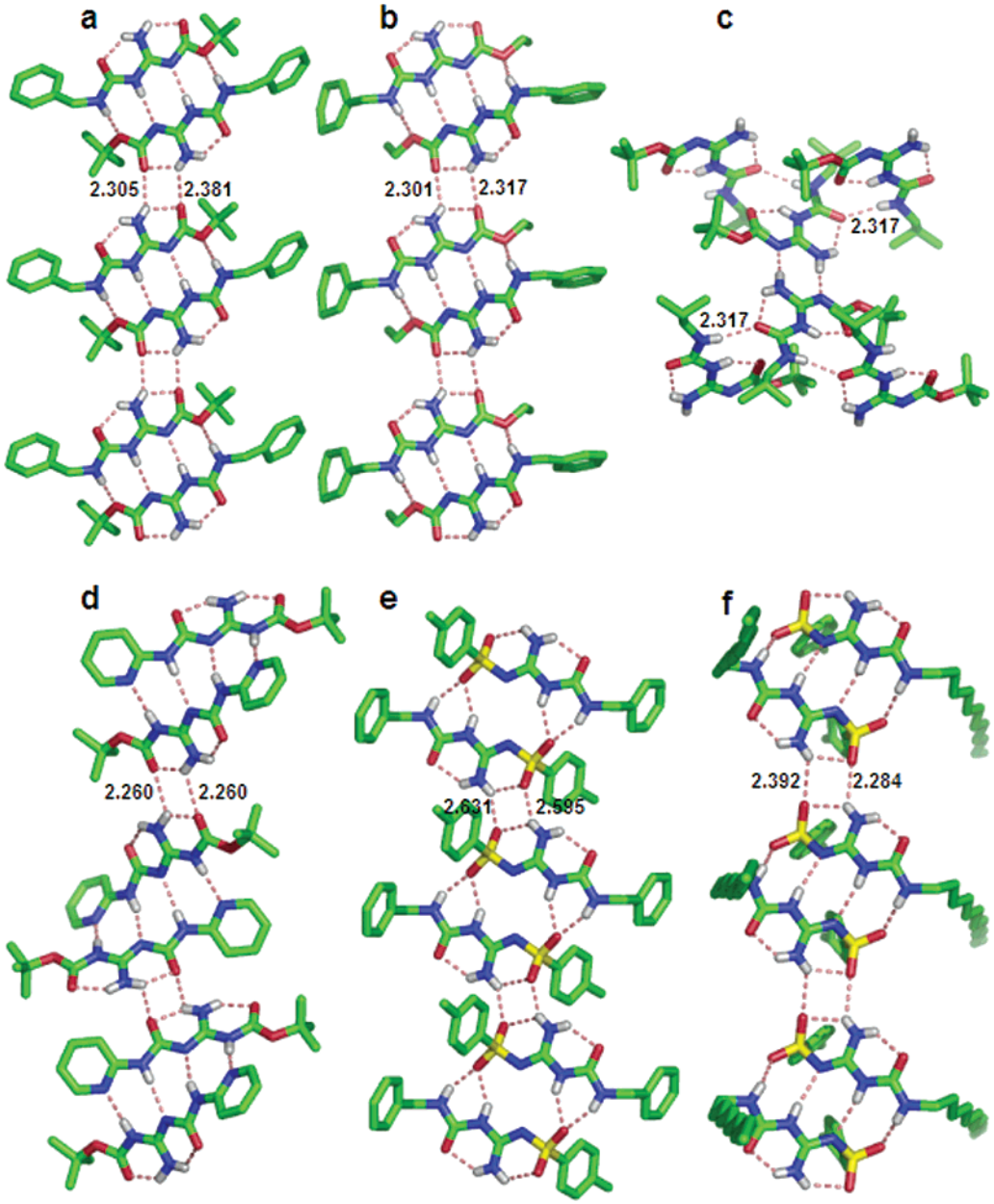


FIGURE 4. Further self-assembly of the dimers **1.1a**−**d** and **2.2a**,**b**. Hydrogen bonding is highlighted in dashes (salmon colored), above which [$R^2_2(4)$]-type hydrogen bond distances (N−H···N and N−H···O) are displayed in Å. All hydrogens, other than those at the hydrogen-bonding sites, and the disordered atoms/rings have been omitted for clarity. Only a single sheet of self-assembled network is shown here. This figure was made using PyMOL.[18]

Remarkably, all the quadruply hydrogen-bonded dimers **1.1a**,**b**,**d** and **2.2a**,**b** undergo further self-assembly using the not-so-common four-membered ring intermolecular hydrogen-bonding interaction,[16,26] forming extended sheetlike supramolecular networks (Figure 4).

Four-membered ring hydrogen bond-mediated self-assembly has been reported in certain nitro anilines,[26] wherein both the hydrogen bond acceptor atoms (oxygen) of nitro group bind a single proton, usually from a secondary aromatic amine, to form a [$R^2_2(4)$]-type[16] four-membered hydrogen-bonded network. The supramolecular assembly of the dimers (**1.1a**,**b**,**d** and **2.2a**,**b**) through the four-membered ring intermolecular hydrogen bonding is characterized by relatively longer hydrogen bonds (d(N−H···O_{avg}) = 2.355 Å), which suggests that additional interactions, presumably from the cooperative hydrophobic interactions of the *N*-urea and *O*-carbamate substituents of the adjacent duplexes, might be involved in stabilizing these extended self-assembled networks. Indeed, such cooperative hydrophobic interactions are known to play a crucial role in aiding the self-assembly of peptide/protein β-sheets containing substantial amounts of hydrophobic amino acid residues.[27] Interestingly, the dimer **1.1c** that lacks predisposition of its N- and O-substituents as in the other cases (**1a**,**b**,**d** and **2a**,**b**) self-assembles in a different fashion, affording a pillar-type supramolecular ensemble (figure **4c**).

(26) Panunto, T. W.; Urbaliczyk-Lipkowska, Z.; Johnson, R. B.; Etter, M. C. *J. Am. Chem. Soc.* **1987**, *109*, 7786−7797.

Summary

Fixing multiple cooperative binding sites in an ideal spatial arrangement on a structurally rigid backbone, constrained by intramolecular hydrogen bonding, is a novel way for facilitating the hydrogen bond-directed synthesis of molecular dimers. In this article, we have demonstrated the ability of the self-assembling constructs **1** and **2**, both of them based on the amidinourea motif, to form molecular dimers, whose structural preorganization has been solely effected by intramolecular hydrogen bonding. It is interesting to note that the molecular dimers **1.1a**−**d** and **2.2a**,**b** undergo further self-assembly, affording supramolecular hydrogen-bonded networks.[28] The ease with which the amidinourea motif can be manipulated to yield a diverse set of molecular dimers and their high propensity for crystallization[14] are noteworthy. With these observations realized, experiments are underway to extend this strategy for the preorganization of much larger linear hydrogen-bonding arrays.[29] Such studies should allow us to further delineate the contributions of cooperative forces on the molecular assembly process such that the construction of organic assemblies akin to those of nanoscale biological complexes may be realized.

Experimental Section

General Procedure: [Amino-(3-benzylureido)-methylene]-carbamic Acid *tert*-Butyl Ester 1a. A mixture of *N*,*N*′-di-boc-guanidine (1.3 g, 5 mmol, 1 equiv) and benzylamine (1.6 mL, 15 mmol, 3 equiv) in dry THF (10 mL) was refluxed with stirring for 12 h. The solvent was evaporated under reduced pressure, and the residue was subjected to purification by column chromatography (50% pet. ether/ethyl acetate, R_f 0.7) to yield a colorless sticky compound that was crystallized from chilled chloroform to yield **1a** (65%). mp 110 °C; IR ($CHCl_3$) ν (cm^{-1}): 3396, 3269, 3013, 2980, 2934, 1647, 1547, 1508, 1454, 1302, 1244, 1148; ^1H NMR (500 MHz, $CDCl_3$): δ 8.65 (br, 3H), 7.33−7.26 (m, 5H), 6.25 (bs, 1H), 4.36 (d, J = 5.5 Hz, 2H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): 158.3, 138.6, 128.5, 127.2, 82.0, 43.7, 28.0; ESI mass: 293.04 ($M^+ + 1$), 586.02 ($2M^+ + 2$); Anal. Calcd for $C_{14}H_{20}N_4O_3$: C, 57.52; H, 6.90; N, 19.16. Found: C, 57.28; H, 7.10; N, 19.32.

[Amino-(3-benzylureido)-methylene]-carbamic Acid Ethyl Ester 1b. To a 1:1 mixture of TFA and DCM (10 mL) was added **1a** (300 mg, 1.0 mmol) at room temperature. After being stirred for 30 min, the reaction mixture was stripped off the volatiles under reduced pressure, and the waxy residue was dissolved in DCM (5 mL). Triethylamine (0.43 mL, 3.1 mmol, 3 equiv) was added to the above reaction mixture, followed by the addition of ethylchloroformate (0.1 mL, 1.0 mmol, 1 equiv). After being stirred overnight, the reaction mixture was diluted with DCM (10 mL) and washed successively with saturated bicarbonate solution and water, and the organic layer was separated and dried over anhydrous Na_2SO_4. Evaporation of DCM under reduced pressure, followed by purification of the crude product by column chromatography (50% petroleum ether/ ethyl acetate, R_f 0.5), gave **1b** as colorless solid (61%) that could be crystallized by diffusion of pet. ether into a solution of the compound in ethyl acetate. mp 139−140 °C; IR ($CHCl_3$) ν (cm^{-1}): 3384, 3288, 3018, 2401, 2361, 1672, 1626, 1547, 1370, 1288, 1231, 1140; ^1H NMR (500 MHz, $CDCl_3$): δ 10.67−8.80 (br, 3H), 7.34−7.25 (m, 5H), 6.41 (bs, 1H), 4.39 (d, J = 5.5 Hz, 2H), 3.99 (bs, 2H), 1.18 (bs, 3H); ^{13}C (125 MHz, $CDCl_3$): 161.7, 160.4, 157.1, 138.1, 128.7, 127.4, 61.3, 43.7, 14.3; ESI mass: 265.20 ($M^+ + 1$), 529.39 ($2M^+ + 1$); Anal. Calcd for $C_{12}H_{16}N_4O_3$: C, 54.54; H, 6.10; N, 21.20. Found: C, 54.38; H, 6.22; N, 21.28.

***N*-[Amino-3-benzylureido)-methylene]-4-methylbenzenesulfonamide 2a. 2a** was synthesized from **1a** (300 mg, 1.0 mmol, 1 equiv), following the same procedure for synthesis of compound **1b**, and using *p*-toluenesulfonyl chloride (196 mg, 1.0 mmol, 1 equiv). Purification was effected by column chromatography (60% petroleum ether/ethyl acetate, R_f 0.7) to yield **2a** as a white solid (60%) that could be crystallized from chilled ethyl acetate. mp: 180−181 °C; IR (Nujol) ν (cm^{-1}): 3377, 3271, 3229, 2924, 2854, 1711, 1633, 1582, 1549, 1456, 1261, 1224, 1155, 1142; ^1H NMR (500 MHz, $CDCl_3$): δ 9.62 (s, 1H), 9.53 (s, 1H), 7.81 (s, 1H), 7.74 (bs, 1H), 7.61 (d, J = 7.9 Hz, 2H), 7.26−7.23 (m, 5H), 7.17 (d, J = 7.9 Hz, 2H), 4.32 (d, J = 5.7 Hz, 2H), 2.42 (s, 3H); ^{13}C (125 MHz, $CDCl_3$): δ 156.8, 154.7, 142.8, 138.8, 137.6, 129.2, 128.3, 127.4, 127.1, 125.8, 43.5, 21.3; ESI mass: 347.09 ($M^+ + 1$), 693.17 ($2M^+ + 1$); Anal. Calcd for $C_{16}H_{18}N_4O_3S$: C, 55.49; H, 5.24; N, 16.18; S, 9.25. Found: C, 55.43; H, 5.33; N, 16.04; S, 8.94.

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Supporting Information Available: Experimental procedures, ^1H, ^{13}C, and DEPT 135 NMR spectra and ESI mass spectra of **1a**−**e** and **2a**,**b** (PDF), and crystallographic data of **1a**−**d** and **2a**,**b** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(28) Crystallographic data for **1a**−**d** and **2a**,**b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 281678 (**1a**), CCDC 281679 (**1b**), CCDC 281680 (**1c**), CCDC 281681 (**1d**), CCDC 281682 (**2a**), and CCDC 281683 (**2b**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.

(29) Self-complementary self-assembling modules with larger (more than six) linear hydrogen-bonding arrays have been reported. See: (a) Mayer, M. F.; Nakashima, S.; Zimmerman, S. C. *Org. Lett.* **2005**, *7*, 3005−3008. (b) Reference 6i.