JOC Article

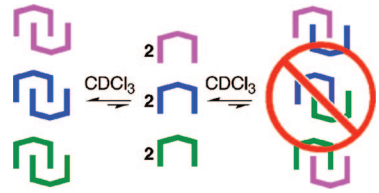
Self-Sorting Molecular Clips

Soumyadip Ghosh,[†] Anxin Wu,*[,‡] James C. Fettinger,[†] Peter Y. Zavalij,[†] and Lyle Isaacs*[,†]

Department of Chemistry and Biochemistry, University of Maryland, College Park, Maryland 20742, and Key Laboratory of Pesticide and Chemical Biology, Ministry of Education, Central China Normal University, Wuhan 430079, People's Republic of China

LIsaacs@umd.edu

Received May 1, 2008



We report the synthesis and characterization of 12 C-shaped methylene-bridged glycoluril dimers (**1**−**12**) bearing H-bonding groups on their aromatic rings. Compounds **1**, **2**, (±)-**4a**, (±)-**5**, (±)-**7**, and **8** form tightly associated homodimers in $CDCl_3$, due to the combined driving force of $\pi-\pi$ and H-bonding interactions. Compounds **2**, (±)-**5**, and **8**, having disparate spatial distribution of their H-bonding groups, display the ability to efficiently distinguish between self and nonself even within three-component mixtures in $CDCl_3$. When the spatial distributions of the H-bonding groups of the molecular clips are similar (e.g., **1** and **2**), a mixture of homodimers and heterodimers is formed. The effect of various structural modifications (e.g., chirality, side chain steric bulk, number and pattern of H-bonds) on the strength of self-assembly and the fidelity of self-sorting are presented. On the basis of these results we prepared self-sorting systems comprising three (e.g., **1**, (±)-**5**, and (±)-**7**) and even four (**2**, (±)-**5**, **9**, and **10**) components. The potential of molecular clips **1**−**12** as robust, functionalizable, self-sorting modules to control the noncovalent interaction network in systems chemistry studies is described.

Introduction

As supramolecular chemistry has continued to develop following the pioneering work of Cram, Lehn, and Pedersen, the focus of much research in the area has shifted from an understanding of the fundamental aspects of noncovalent interactions, molecular recognition, and self-assembly and toward the use of such information to construct systems with function.[1] For example, supramolecular chemistry has provided new approaches toward chemical sensing ensembles, discovery via dynamic combinatorial chemistry, drug delivery, membrane transport agents, DNA nanotechnology, control of otherwise unfavorable chemical reactions, and supramolecular polymers.[2,3] In all of these applications, the ready availability of robust and easily functionalized modules capable of specific noncovalent interactions (e.g., $\pi-\pi$, metal−ligand, and H-bonding modules) with their targets in organic or aqueous solution has proved invaluable.[4–6] For example, quadruple hydrogen-bonding modules with high values of K_a have been used in the formation of high-molecular-weight supramolecular polymers.[6] To date, however, the majority of such functional systems have been demonstrated to operate only in isolation and not as components of more complex chemical or biological systems.

[†] University of Maryland.
[‡] Central China Normal University.

(1) Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1009–1020. Lehn, J. M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 89–112. Pedersen, C. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1021–1027.

(2) Corbett, P. T.; Leclaire, J.; Vial, L.; West, K. R.; Wietor, J.-L.; Sanders, J. K. M.; Otto, S. *Chem. Rev.* **2006**, *106*, 3652–3711. Lehn, J.-M. *Chem. Eur. J.* **1999**, *5*, 2455–2463. Wright, A. T.; Anslyn, E. V. *Chem. Soc. Rev.* **2006**, *35*, 14–28. Davis, A. P.; Sheppard, D. N.; Smith, B. D. *Chem. Soc. Rev.* **2007**, *36*, 348–357. Seeman, N. C. *Mol. Biotechnol.* **2007**, *37*, 246–257. Jon, S. Y.; Ko, Y. H.; Park, S. H.; Kim, H.-J.; Kim, K. *Chem. Commun.* **2001**, 1938–1939. Sisson, A. L.; Shah, M. R.; Bhosale, S.; Matile, S. *Chem. Soc. Rev.* **2006**, *35*, 1269–1286. Haag, R.; Kratz, F. *Angew. Chem., Int. Ed.* **2006**, *45*, 1198–1215. Yoshizawa, M.; Tamura, M.; Fujita, M. *Science* **2006**, *312*, 251–254. Pluth, M. D.; Bergman, R. G.; Raymond, K. N. *Science* **2007**, *316*, 85–88.

(3) Pollino, J. M.; Weck, M. *Chem. Soc. Rev.* **2005**, *34*, 193–207.

(4) Fujita, M.; Umemoto, K.; Yoshizawa, M.; Fujita, N.; Kusukawa, T.; Biradha, K. *Chem. Commun.* **2001**, *50*, 9–518. Seidel, S. R.; Stang, P. J. *Acc. Chem. Res.* **2002**, *35*, 972–983. Corbin, P. S.; Lawless, L. J.; Li, Z.; Ma, Y.; Witmer, M. J.; Zimmerman, S. C. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 5099–5104. Pollino, J. M.; Stubbs, L. P.; Weck, M. *J. Am. Chem. Soc.* **2004**, *126*, 563–567.

(5) Balzani, V.; Credi, A.; Raymo, F. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2000**, *39*, 3348–3391.

(6) Sijbesma, R. P.; Meijer, E. W. *Chem. Commun.* **2003**, 5–16.

10.1021/jo8009424 CCC: $40.75
Published on Web 06/28/2008

In contrast to biologists, computer scientists, and engineers—who embrace the need to study complex systems and appreciate the insights that may be gained from a systems level approach—chemists have been comparably slow to approach the study of complex multicomponent systems. This difference has begun to subside in recent years with the development of powerful new analytical tools that provide approaches to previously intractable problems. This group of scientists—drawn from numerous fields—are beginning to define an area now known as *systems chemistry*.[7] Systems chemists study complex multicomponent systems that exhibit emergent properties that go beyond those of their components. Some systems chemists take their inspiration from biology and design systems that exhibit properties such as self-replication,[8] whereas others add new components to existing biological systems in an attempt to control biological function. Other systems chemists take inspiration from technology and aim to integrate individual molecular devices into more complex molecular machines.[5,9]

We have based our entry into systems chemistry on the realization that all of these biological or technological systems depend critically on the availability of robust, easily functionalized supramolecular modules (vide supra) that operate not only in isolation but also as components of more complex systems. The behavior of such systems is controlled by the network of binary and higher order interactions between the constituent molecules. Rather than being governed by all possible (e.g., random) sets of interactions, such systems tend to organize themselves into a smaller number of sets of interacting molecules with interconnections between these sets that respond to external stimuli from their environment. As such, the ability of the constituents of such systems to efficiently distinguish between self and nonself is critical. We previously showed that a mixture comprising the components of eight well-known aggregates from the literature is capable of efficiently distinguishing between self and nonself even within the mixture—on the basis of H-bond pattern and geometrical distribution—and undergoes a high-fidelity self-sorting process.[10] Subsequently, we have developed self-sorting systems based on host−guest interactions (social self-sorting), those that display well-defined kinetic and thermodynamic self-sorted states, and shown how such systems can be made to respond to chemical stimuli (e.g., guest addition or pH change).[11] In this paper we investigate the ability of a series of glycoluril-derived molecular clips[12–14] (**1**−**12**)—several of which undergo tight dimerization ($K_a \geq 10^6$ M^{-1}) in $CDCl_3$ solution—to act as robust, functionalizable, self-sorting supramolecular modules.[15,16] We envision that such supramolecular modules will greatly expand the toolbox available to systems chemists for the construction of complex and functional systems.

Results and Discussion

This section is organized as follows. First, we present the design and synthesis of molecular clips **1**−**12**. Next, we detail the dimeric aggregates formed by these molecular clips in $CDCl_3$ solution and the solid state. Subsequently, we describe the ability of these compounds to undergo self-sorting within two-,[13] three-, and four-component mixtures. Within these complex mixtures, we investigate the influence of chirality, side chain steric bulk, and electronic effects on the strength of dimerization and ultimately the fidelity of self-sorting.

Design and Synthesis of the Chemical Components Used in This Study. Chart 1 shows the chemical structures of the 12 C-shaped methylene-bridged glycoluril dimers used in this paper. The key structural features in the design of molecular clips **1**−**12** were as follows. First, all 12 clips possess two roughly parallel aromatic walls separated by ∼7 Å which define a cleft that promotes dimerization in chloroform driven by $\pi-\pi$ interactions.[13,14,17] Even though $\pi-\pi$ interactions have preferred geometries (e.g., edge-to-face or offset face-to-face),[18] we thought that dimeric molecular clips driven solely by $\pi-\pi$ interactions might exist as an ensemble of conformational isomers that differ in the relative orientation of the molecular clips with respect to each other (Figure 1). Second, the rigid

(7) Ludlow, R. F.; Otto, S. *Chem. Soc. Rev.* **2008**, *37*, 101–108. Corbett, P. T.; Sanders, J. K. M.; Otto, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 8858–8861. Kindermann, M.; Stahl, I.; Reimold, M.; Pankau Wolf, M.; von Kiedrowski, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 6750–5. Sarma, R. J.; Nitschke, J. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 377–380. Nitschke, J. R. *Acc. Chem. Res.* **2007**, *40*, 103–112.

(8) Wintner, E. A.; Conn, M. M.; Rebek, J. J. *Acc. Chem. Res.* **1994**, *27*, 198–203. Bachmann, P. A.; Luisi, P. L.; Lang, J. *Nature* **1992**, *357*, 57–9. Terfort, A.; Von Kiedrowski, G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 654–656. Lee, D. H.; Severin, K.; Yokobayashi, Y.; Ghadiri, M. R. *Nature* **1997**, *390*, 591–594. Sievers, D.; von Kiedrowski, G. *Chem. Eur. J.* **1998**, *4*, 629–641. Yao, S.; Ghosh, I.; Zutshi, R.; Chmielewski, J. *Nature* **1998**, *396*, 447–450. Issac, R.; Chmielewski, J. *J. Am. Chem. Soc.* **2002**, *124*, 6808–6809. Kassianidis, E.; Philp, D. *Angew. Chem., Int. Ed.* **2006**, *45*, 6344–6348.

(9) Kay, E. R.; Leigh, D. A.; Zerbetto, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 72–191.

(10) Wu, A.; Isaacs, L. *J. Am. Chem. Soc.* **2003**, *125*, 4831–4835.

(11) Mukhopadhyay, P.; Wu, A.; Isaacs, L. *J. Org. Chem.* **2004**, *69*, 6157–6164. Liu, S.; Ruspic, C.; Mukhopadhyay, P.; Chakrabarti, S.; Zavalij, P. Y.; Isaacs, L. *J. Am. Chem. Soc.* **2005**, *127*, 15959–15967. Mukhopadhyay, P.; Zavalij, P. Y.; Isaacs, L. *J. Am. Chem. Soc.* **2006**, *128*, 14093–14102. Liu, S.; Zavalij, P. Y.; Lam, Y.-F.; Isaacs, L. *J. Am. Chem. Soc.* **2007**, *129*, 11232–11241. Chakrabarti, S.; Mukhopadhyay, P.; Lin, S.; Isaacs, L. *Org. Lett.* **2007**, *9*, 2349–2352.

(12) For leading examples of molecular clips and tweezers, see: Rowan, A. E.; Elemans, J. A. A. W.; Nolte, R. J. M. *Acc. Chem. Res.* **1999**, *32*, 995–1006. Zimmerman, S. C. *Top. Curr. Chem.* **1993**, *165*, 71–102. Klaerner, F.-G.; Kahlert, B. *Acc. Chem. Res.* **2003**, *36*, 919–932. Harmata, M. *Acc. Chem. Res.* **2004**, *37*, 862–873. Jiang, H.; Leger, J.-M.; Guionneau, P.; Huc, I. *Org. Lett.* **2004**, *6*, 2985–2988. Chiang, P.-T.; Cheng, P.-N.; Lin, C.-F.; Liu, Y.-H.; Lai, C.-C.; Peng, S.-M.; Chiu, S.-H. *Chem. Eur. J.* **2006**, *12*, 865–876. Petitjean, A.; Khoury, R. G.; Kryritsakas, N.; Lehn, J.-M. *J. Am. Chem. Soc.* **2004**, *126*, 6637–6647. Artacho, J.; Nilsson, P.; Bergquist, K.-E.; Wendt, O. F.; Wärnmark, K. *Chem. Eur. J.* **2006**, *12*, 2692–2701. Hu, S.-L.; She, N.-F.; Yin, G.-D.; Guo, H.-Z.; Wu, A.-X.; Yang, C.-L. *Tetrahedron Lett.* **2007**, *48*, 1591–1594.

(13) Wu, A.; Chakraborty, A.; Fettinger, J. C.; Flowers, R. A., II; Isaacs, L. *Angew. Chem., Int. Ed.* **2002**, *41*, 4028–4031.

(14) Wu, A.; Mukhopadhyay, P.; Chakraborty, A.; Fettinger, J. C.; Isaacs, L. *J. Am. Chem. Soc.* **2004**, *126*, 10035–10043.

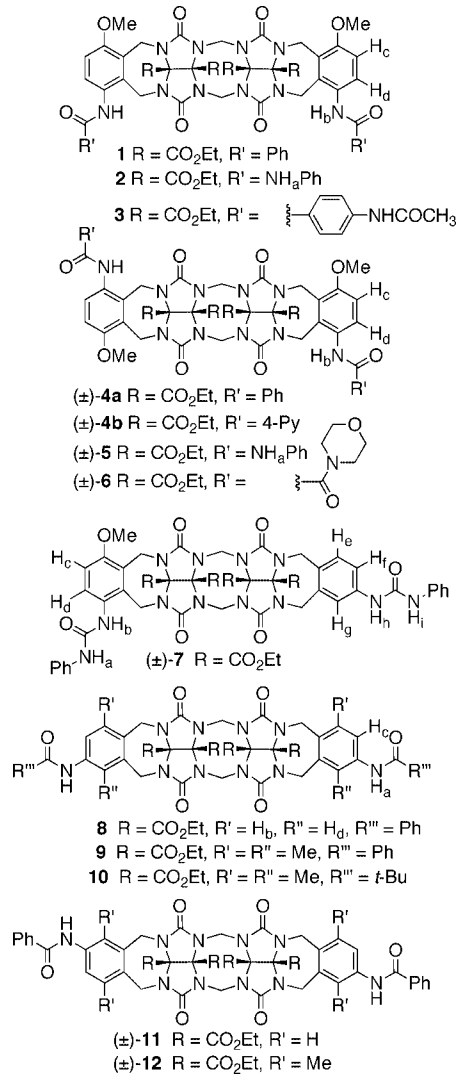
(15) For leading examples of self-sorting, see: Rowan, S. J.; Hamilton, D. G.; Brady, P. A.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1997**, *119*, 2578–2579. Jolliffe, K. A.; Timmerman, P.; Reinhoudt, D. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 933–937. Taylor, P. N.; Anderson, H. L. *J. Am. Chem. Soc.* **1999**, *121*, 11538–11545. Bilgicer, B.; Xing, X.; Kumar, K. *J. Am. Chem. Soc.* **2001**, *123*, 11815–11816. Hwang, I.-W.; Kamada, T.; Ahn, T. K.; Ko, D. M.; Nakamura, T.; Tsuda, A.; Osuka, A.; Kim, D. *J. Am. Chem. Soc.* **2004**, *126*, 16187–16198. Burd, C.; Weck, M. *Macromolecules* **2005**, *38*, 7225–7230. Uzun, O.; Xu, H.; Jeoung, E.; Thibault, R. J.; Rotello, V. M. *Chem. Eur. J.* **2005**, *11*, 6916–6920. Kamada, T.; Aratani, N.; Ikeda, T.; Shibata, N.; Higuchi, Y.; Wakamiya, A.; Yamaguchi, S.; Kim, K. S.; Yoon, Z. S.; Kim, D.; Osuka, A. *J. Am. Chem. Soc.* **2006**, *128*, 7670–7678. Xu, H.; Hong, R.; Lu, T.; Uzun, O.; Rotello, V. M. *J. Am. Chem. Soc.* **2006**, *128*, 3162–3163. He, Y.; Tian, Y.; Chen, Y.; Ribbe, A. E.; Mao, C. *Chem. Commun.* **2007**, 165–167. Legrand, Y.-M.; Van der Lee, A.; Barboiu, M. *Inorg. Chem.* **2007**, *46*, 9540–9547. Plutowski, U.; Jester, S. S.; Lenhert, S.; Kappes, M. M.; Richert, C. *Adv. Mater.* **2007**, *19*, 1951–1956. Hutin, M.; Cramer, C. J.; Gagliardi, L.; Shahi, A. R. M.; Bernardinelli, G.; Cerny, R.; Nitschke, J. R. *J. Am. Chem. Soc.* **2007**, *129*, 8774–8780. Braekers, D.; Peters, C.; Bogdan, A.; Rudzevich, Y.; Boehmer, V.; Desreux, J. F. *J. Org. Chem.* **2008**, *73*, 701–706. Barrett, E. S.; Dale, T. J.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2008**, *130*, 2344–2350. Shi, X.; Fettinger, J. C.; Davis, J. T. *J. Am. Chem. Soc.* **2001**, *123*, 6738–6739. Cai, M.; Shi, X.; Sidorov, V.; Fabris, D.; Lam, Y.-F.; Davis, J. T. *Tetrahedron* **2002**, *58*, 661–671. Schnarr, N. A.; Kennan, A. J. *J. Am. Chem. Soc.* **2002**, *124*, 9779–9783. Hirst, A. R.; Huang, B.; Castelletto, V.; Hamley, I. W.; Smith, D. K. *Chem. Eur. J.* **2007**, *13*, 2180–2188.

(16) Saur, I.; Scopelliti, R.; Severin, K. *Chem. Eur. J.* **2006**, *12*, 1058–1066.

(17) Isaacs, L.; Witt, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 1905–1907.

(18) Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1210–1250.

CHART 1. Chemical Structures of Molecular Clips Used in This Paper



geometry of the molecular clips and the straightforward functionalization of their *o*-xylylene sidewalls was utilized to display H-bonding functional groups (e.g., amide, urea, oxamide) in well-defined relative orientations. We envisioned that interactions between these H-bonding arms could be used to drive dimerization in $CDCl_3$ solution and also result in the selection of a single well-defined conformation from the conformational ensemble (Figure 1) that satisfied the geometric requirements of both the H-bonding and $\pi-\pi$ interactions.[14]

The synthesis of compounds **1**−**12** is shown in Scheme 1. For the preparation of compounds **1**−**6**, we used the previously reported dinitro compounds **13** and (±)-**14** as starting materials.[17,19] The separate catalytic hydrogenation of **13** and (±)-**14** to the corresponding air-sensitive diamines proceeded smoothly in dimethylformamide (DMF) as solvent. The crude diamines were transformed into the corresponding amides and ureas by reaction with acid chlorides and isocyanates in CH_2Cl_2 at room temperature to deliver **1**−**6** in 43−90% yield. To prepare compounds **8** and **11**, which contain amide substituents at the 4-position of the *o*-xylylene sidewalls, we needed to prepare

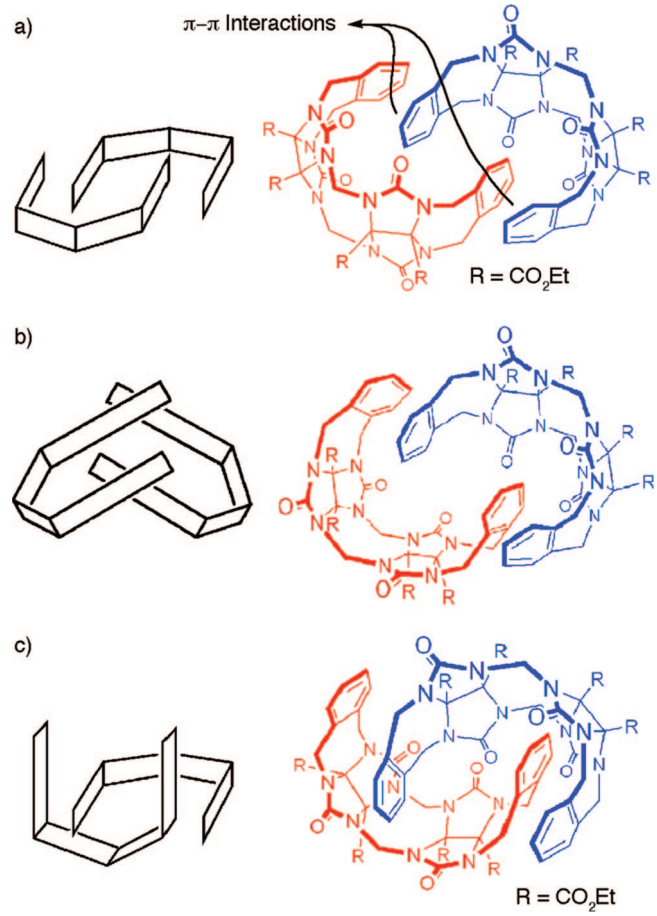


FIGURE 1. Schematic representation of three members of the conformational ensemble open to dimeric molecular clips driven solely by $\pi-\pi$ interactions: (a) in register geometry; (b) in skewed geometry; (c) in perpendicular geometry.

(±)-**17**. For the synthesis of (±)-**17**, we first performed the free radical bromination of 4-nitro-*o*-xylene using *N*-bromosuccinimide in 1,2-dichloroethane, which gave **15** in 47% yield.[20] Alkylation of **16** with compound **15** (*t*-BuOK, DMSO) gave (±)-**17** in 22% yield. Compound (±)-**17** was dimerized by acid-catalyzed condensation with paraformaldehyde in the presence of *p*-toluenesulfonic acid (PTSA) in $ClCH_2CH_2Cl$ to give **18** and (±)-**19** in 23% and 20% yields, respectively.[19] After chromatographic separation, regioisomers **18** and (±)-**19** were separately reduced and then acylated with benzoyl chloride to give **8** and (±) **11** in 73% and 76% yields, respectively.

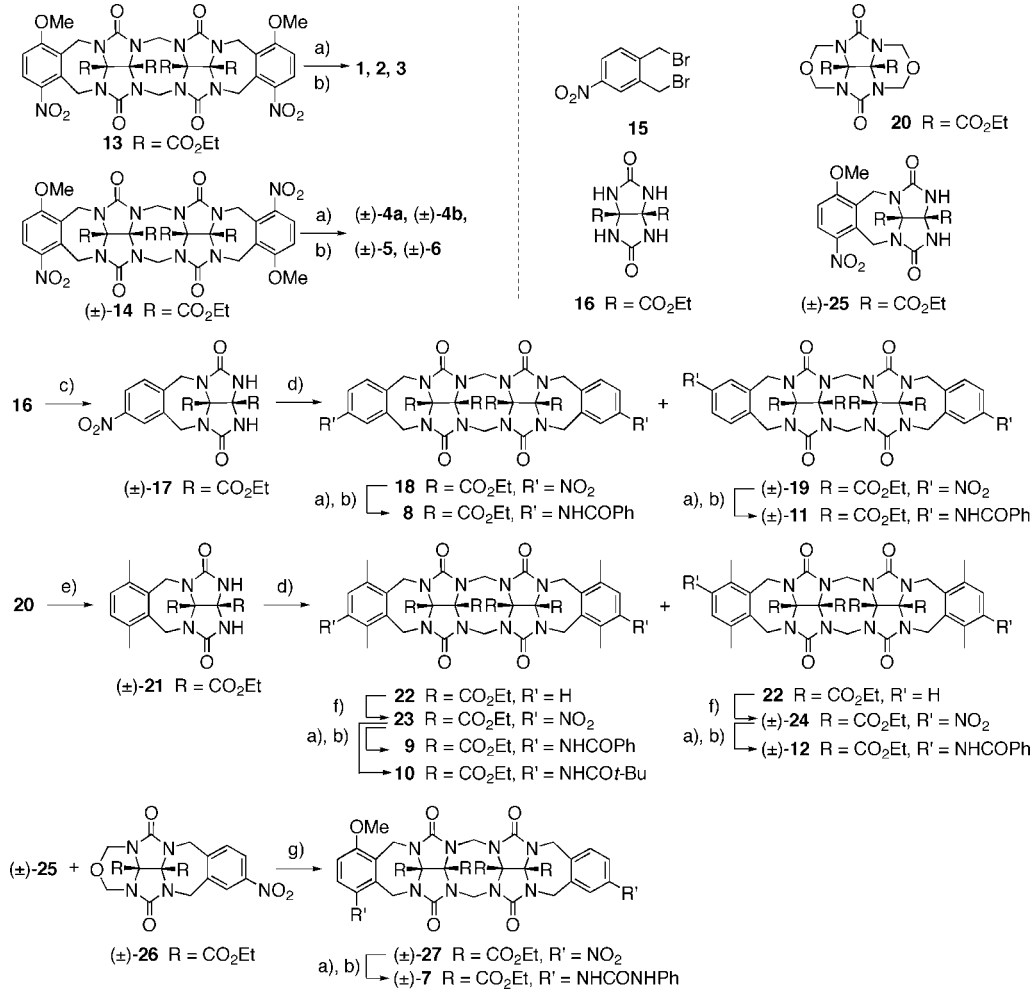
Compounds **9**, **10**, (±)-**12**, and (±)-**7** were synthesized by related procedures. Somewhat surprisingly, we found that heating **20** with PTSA in *p*-xylene gave **21** by extrusion of one of the CH_2OCH_2 bridges in 36% yield. Acid-catalyzed condensation of compound **21** with paraformaldehyde gave dimer **22** in 78% yield. Compound **22** was nitrated (TFA, HNO_3) to give a mixture of regioisomers **23** and (±)-**24** in 42% and 38% yields, respectively. After chromatographic separation, regioisomers **23** and (±)-**24** were separately reduced and then acylated with the appropriate acid chloride to give **9**, **10**, and (±)-**12** in 65−75% yields. Condensation of (±)-**25** with cyclic ether (±)-**26**[21] in presence of PTSA in $ClCH_2CH_2Cl$ gave a mixture of two dinitro

(19) Wu, A.; Chakraborty, A.; Witt, D.; Lagona, J.; Damkaci, F.; Ofori, M. A.; Chiles, J. K.; Fettinger, J. C.; Isaacs, L. *J. Org. Chem.* **2002**, *67*, 5817–5830.

(20) Wang, Z.-G.; Zhou, B.-H.; Chen, Y.-F.; Yin, G.-D.; Li, Y.-T.; Wu, A.-X.; Isaacs, L. *J. Org. Chem.* **2006**, *71*, 4502–4508.

(21) Qin, S.; Yin, G. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2005**, *E61*, o3164–o3165.

SCHEME 1. Synthesis of Molecular Clips 1−12[a]



[a] Conditions: (a) Pd/C, H_2, DMF; (b) PhNCO or R′COCl, Et_3N, CH_2Cl_2; (c) **15**, *t*-BuOK, DMSO; (d) PTSA, $(CH_2O)_n$, $ClCH_2CH_2Cl$, reflux; (e) PTSA, *p*-xylene, reflux; (f) TFA, HNO_3; (g) PTSA, $ClCH_2CH_2Cl$, reflux.

compounds. Chromatographic purification gave (±)-**27** in low yield (13%), which was reduced (Pd/C, H_2, DMF) to the corresponding diamine followed by reaction with phenyl isocyanate to give (±)-**7** in 39% yield.

Molecular Clips Form Homodimers in $CDCl_3$. The ^1H NMR spectra of **1**, **2**, (±)-**4a**, and (±)-**5** in DMSO-d_6 show a single set of resonances due to the presence of symmetry-equivalent halves, which indicates that these molecules are monomeric in DMSO-d_6.[22] In $CDCl_3$, however, we observe a doubling of resonances in their ^1H NMR spectra along with significant anisotropic effects, which suggests that these molecules exist as dimers (Figure 2). For example, although only two N−H resonances (H_a and H_b) were observed in DMSO-d_6 for **2**, we observed four resonances in $CDCl_3$ (H_a, $H_{a'}$, H_b, and $H_{b'}$), which correspond to the two different N−H···O H-bonds in homodimer **2**·**2**. Similarly, in the monomeric form the aromatic protons of **2** (H_c and H_d) give rise to a single set of resonances due to the presence of a mirror plane in the molecule. When **2** undergoes dimerization to yield **2**·**2**, this mirror plane no longer exists. One set of aromatic rings resides in the interior of the dimer, whereas the other set is on the exterior. The chemical shift of the aromatic protons ($H_{c'}$ and $H_{d'}$) on the internal aromatic wall of **2**·**2** resonate upfield relative to the protons of the external aromatic ring (H_c and H_d) because they

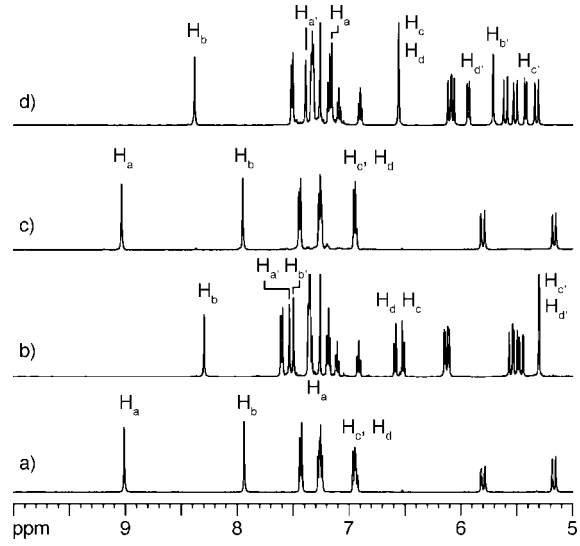


FIGURE 2. Portions of the ^1H NMR (500 MHz, room temperature) spectra recorded for (a) **2** in DMSO-d_6, (b) **2**·**2** in $CDCl_3$, (c) (±)-**5** in DMSO-d_6, and (d) (+)-**5**·(−)-**5** in $CDCl_3$.

(22) We did not observe any changes in chemical shifts over the 10−0.1 mM concentration range. This rules out the possibility of a fast monomer−dimer exchange as the cause of a single set of resonances.

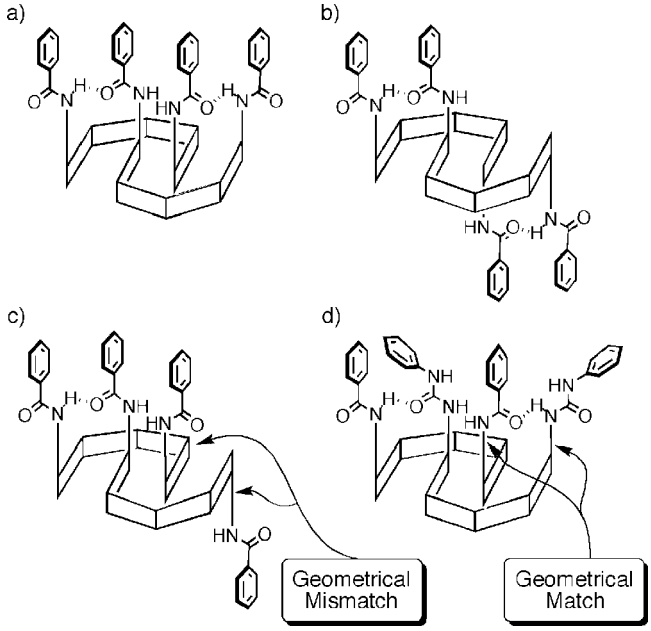


FIGURE 3. Schematic representation of the concept of geometrical match versus geometrical mismatch: (a) **1·1**; (b) (+)-**4a**·(−)-**4a**; (c) hypothetical diastereomeric aggregate formed by (±)-**1·4a**; (d) racemic heterodimer (±)-**1·2**.

are in the shielding region of *two* neighboring aromatic rings. Similar diagnostic features were observed in the ^{1}H NMR of **1·1**, (+)-**4a**·(−)-**4a**, and (+)-**5**·(−)-**5** in $CDCl_3$.

We performed ^{1}H NMR dilution experiments to determine the self-association constant (K_s) for the dimeric aggregation. Remarkably, the chemical shifts observed for dimers **1·1**, **2·2**, (+)-**4a**·(−)-**4a**, and (+)-**5**·(−)-**5** do not change when the concentration is decreased from 10 mM and 50 μM, indicating their high thermodynamic stability. If we assume that we could detect changes in the chemical shifts due to 10% monomer, then we can place a lower limit on the of the value of K_s ($K_s > 9 \times 10^5$ M^{-1}, $\Delta G < -8.1$ kcal mol^{-1}). Such a high thermodynamic stability was not anticipated, given that these dimeric aggregates benefit from a mere two H-bonds. We surmise that the high thermodynamic stability of these aggregates is due to the cumulative effect of $\pi-\pi$ interactions and H-bonds. The concentration invariance and distinct pattern of anisotropic effects in the ^{1}H NMR spectra of dimers **1·1**, **2·2**, (+)-**4a**·(−)-**4a**, and (+)-**5**·(−)-**5** indicate that the combined driving force and geometrical constraints of $\pi-\pi$ interactions and H-bonds are capable of selecting a single member of the complex conformational ensemble open to dimeric molecular clips (Figure 1).

Concept of Geometrical Match and Mismatch. As described above, compounds **1**, **2**, (±)-**4a**, and (±)-**5** undergo strong homodimerization in $CDCl_3$ driven by $\pi-\pi$ interactions and H-bonds. We previously investigated their recognition behavior in binary mixtures of **1** and (±)-**4a** or **2** and (±)-**5** and observed the phenomenon of self-sorting.[13] We attribute this high preference for self-sorting—heterodimers ((±)-**1·4a** or (±)-**2·5**) were not observed by ^{1}H NMR—to a geometrical mismatch between the H-bonding arms **1** and (±)-**4a** or **2** and (±)-**5** in the hypothetical heterodimers (Figure 3). The hypothetical heterodimer (±)-**1·4a**, for example, benefits from $\pi-\pi$ interactions and only a single H-bond, as opposed to $\pi-\pi$ interactions and at least two H-bonds in homodimers **1·1** and (+)-**4a**·(−)-**4a** (Figure 3). Conversely, when an equimolar

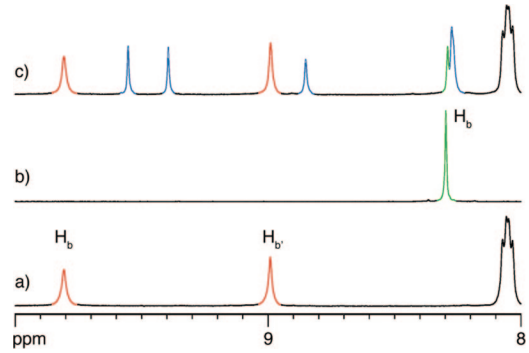


FIGURE 4. Portions of the ^{1}H NMR (2.5 mM, 500 MHz, $CDCl_3$, room temperature) spectra recorded for (a) **1·1**, (b) **2·2**, and (c) a mixture of **1·1**, **2·2**, and (±)-**1·2**. Resonances for the amide N−H groups are color coded as follows: **1·1**, red; **2·2**, green; (±)-**1·2**, blue.

mixture of **1** and **2** with common spatial distribution of their H-bonding arms was prepared in $CDCl_3$, we observed a roughly statistical mixture of homodimers **1·1** and **2·2** and heterodimer (±)-**1·2** by ^{1}H NMR (Figure 4). Similarly, when we analyzed a mixture of (±)-**4a** and (±)-**5** by ^{1}H NMR, a mixture of two heterochiral homodimers ((+)-**4a**·(−)-**4a** and (+)-**5**·(−)-**5**) and a racemic mixture of heterochiral heterodimers ((+)-**4a**·(−)-**5** and (−)-**4a**·(+)-**5**) were observed (Supporting Information). On the basis of this result, we hypothesized that subtle differences in the spatial orientation of H-bonding groups on the edges of the *o*-xylylene rings of these molecular clips might endow these compounds with the ability to efficiently distinguish between self and nonself within binary and higher order mixtures. As such, we anticipated that this class of molecular clips based on methylene-bridged glycoluril dimers might be robust, functionalizable, and self-sorting (e.g., orthogonal) components for the construction of complex chemical systems.

X-ray Crystal Structures of 1, 2, (±)-4b, and (±)-5. Although the ^{1}H NMR experiments mentioned in the previous section clearly support the formation of dimeric aggregates, additional evidence of dimer formation was obtained from the X-ray crystal structures of **1**, **2**, (±)-**4b**, and (±)-**5**. Interestingly, all four molecular clips form dimers in the solid state. All four dimers—**1·1**, **2·2**, (+)-**4b**·(−)-**4b**, and (+)-**5**·(−)-**5**—benefit from $\pi-\pi$ interactions between the substituted *o*-xylylene walls. All of them also benefit from two H-bonds between the external amide (urea) N−H groups and internal amide (urea) C=O groups and secondary electrostatic interactions. Several other features of the geometries of these dimers in the solid state are noteworthy. For example, the pendant benzoyl groups in dimers **1·1** and **2·2** are displayed in a nearly collinear orientation on a single face of the dimer (Figure 5a,b). An additional level of complexity is present for the case of chiral but racemic molecular clips (±)-**4b** and (±)-**5**, where both homochiral dimerization (e.g., (+)-**4b**·(+)-**4b** and (−)-**4b**·(−)-**4b**) and heterochiral dimerization (e.g., (+)-**4b**·(−)-**4b**) are conceivable.[23] In the crystal we only observe the formation of heterochiral dimers (Figure 5c,d). We attribute this result to the geometrical mismatch between the H-bonding groups in the hypothetical homochiral homodimer. All these observations in the solid state determined by X-ray crystallography are consis-

(23) Rudi, A.; Kopilov, J.; Goldberg, I.; Kol, M. *J. Am. Chem. Soc.* **2002**, *124*, 5449–5456. Marguly, E.; McDonald, R.; Branda, N. R. *Org. Lett.* **2000**, *2*, 3169–3172. Maeda, C.; Kamada, T.; Aratani, N.; Osuka, A. *Coord. Chem. Rev.* **2007**, *251*, 2743–2752. Telfer, S. G.; Sato, T.; Kuroda, R.; Lefebvre, J.; Leznoff, D. B. *Inorg. Chem.* **2004**, *43*, 421–429.

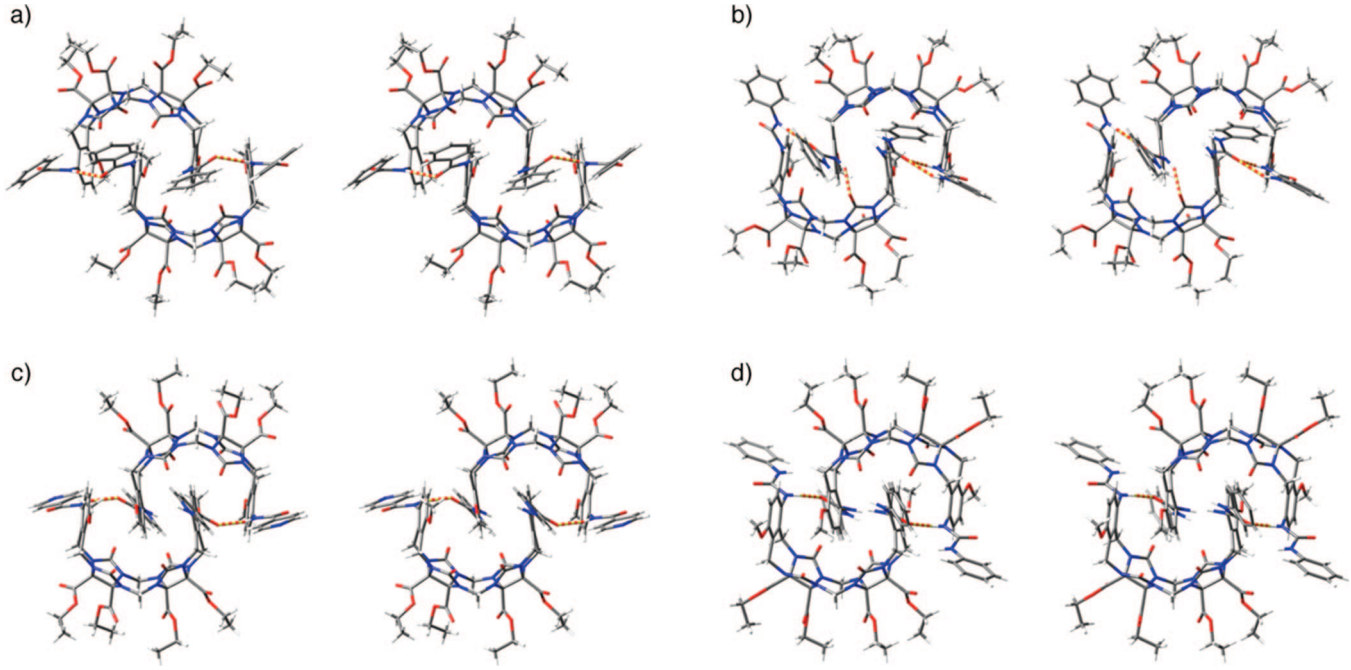


FIGURE 5. Cross-eyed stereoviews of the molecular structures of (a) **1**·**1**, (b) **2**·**2**, (c) (+)-**4b**·(−)-**4b**, and (d) (+)-**5**·(−)-**5** in the crystal. Color coding: C, gray; H, white; N, blue; O, red; H-bonds, yellow-red striped.

tent with their ^{1}H NMR spectra in $CDCl_3$, and we suggest that **1**, **2**, (±)-**4a**, and (±)-**5** are isostructural in the solid state and in solution.[14] The X-ray crystal structures of **1**, **2**, (±)-**4b**, and (±)-**5** also helps us to rationalize the behavior of these molecules within binary and higher order mixtures (vide infra).

Design of Molecular Clips for Three- and Four-Component Self-Sorting Systems. The high selectivity we observed during the self-recognition of **2** and (±)-**5** in a binary mixture of molecular clips and the lack of self-selectivity for mixtures of **1** and **2** or (±)-**4a** and (±)-**5** inspired us to consider situations that fall between these two extreme cases guided by a series of questions. What happens to the strength of dimeric aggregation and fidelity of self-sorting when the H-bonding groups are moved around the edges of the substituted *o*-xylylene walls? Will more complex mixtures of molecular clips (e.g., three or four components) constitute self-sorting systems if each clip has a distinct spatial arrangement of its H-bonding arms? How efficiently can a chiral molecular clip distinguish between itself, its enantiomer, and achiral molecular clips? We were also interested to investigate the effect of various structural modifications (e.g., substituents, steric bulk, number and pattern of H-bonds) on self-assembly and self- versus nonself recognition behavior in a multicomponent mixture that would impact their use as components for advanced applications (e.g., stimuli responsive supramolecular polymers) and the topology of their network interactions[16] when utilized as parts of more complex (bio)molecular systems. To address these questions, we synthesized compounds **3**, **6**, and **7**−**12** and studied their self-association and self-sorting properties in $CDCl_3$ solution.

Three-Component Self-Sorting System. As a first attempt to assess the ability of more subtle geometrical changes to direct self-sorting processes, we prepared **8**, which as opposed to **1**−**6** has PhCONH groups on the tips of its *o*-xylylene sidewalls. Similar to the cases for **1**, **2**, (±)-**4a** and (±)-**5**, compound **8** exhibits a single set of resonances in its ^{1}H NMR spectrum in DMSO-d_6—indicative of a monomer —but two sets of resonances in $CDCl_3$ indicative of dimer formation (Figure 6).

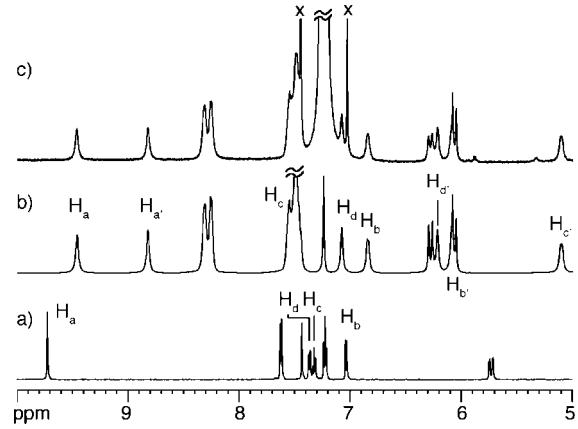


FIGURE 6. Portion of the ^{1}H NMR (500 MHz, room temperature) spectrum recorded for (a) **8** in DMSO-d_6, (b) **8**·**8** (10 mM in $CDCl_3$), and (c) **8**·**8** (50 μM in $CDCl_3$). × = $^{13}CHCl_3$.

Interestingly, the dimeric aggregate **8**·**8** does not undergo significant dissociation down to 50 μM, which establishes a high thermodynamic stability ($K_a > 10^6$ M^{-1}) for this dimer. We were fortunate to obtain an X-ray crystal structure of **8**·**8**, which shows a number of interesting features (Figure 7a). In the dimeric aggregate **8**·**8**, the clips are skewed relative to one another (see Figure 1b) in such a way that the aggregate benefits from $\pi-\pi$ interactions as well as four H-bonds (Figure 8). The amide N−H groups on the internal aromatic rings form H-bonds with the ureidyl C═O of a glycoluril ring on the opposing clip, whereas the external amide N−H groups form H-bonds with the internal amide C═O groups. On the basis of the distinct geometries observed for **2**·**2**, (+)-**5**·(−)-**5**, and **8**·**8**, we wondered whether a mixture of these three molecular clips would undergo high-fidelity self-sorting.

The high level of enantioselectivity exhibited by (+)-**5**·(−)-**5** and skewing observed in the X-ray structure of **8**·**8** led us to combine these clips with **2**·**2** for the next set of experiments. Initially we examined the behavior of the three binary mixtures

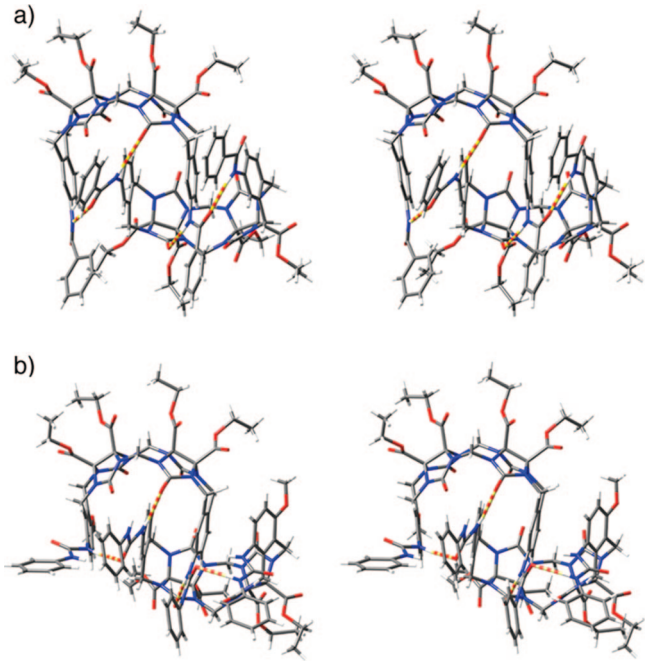


FIGURE 7. Cross-eyed stereoviews of the molecular structures of (a) **8·8** and (b) (+)-**7**·(+)-**7** in the crystal. Color coding: C, gray; H, white; N, blue; O, red; H-bonds, yellow-red striped.

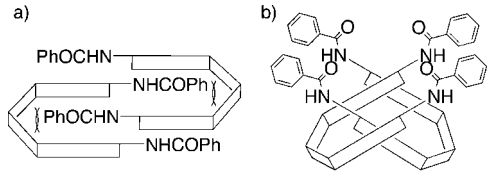


FIGURE 8. Schematic representations of the shapes of **8·8**: (a) steric interaction in the head-to-head form; (b) skewed geometry that avoids steric interactions.

(e.g., **2·2** and (+)-**5**·(−)-**5** or **2·2** and **8·8** or (+)-**5**·(−)-**5** and **8·8**) and were delighted to observe a simple superimposition of the ^{1}H NMR spectra of the constituent homodimeric aggregates (Supporting Information) in each case. These results indicate that these three molecular clips possess the ability to efficiently distinguish between self and nonself. Accordingly, we next constructed the three-component mixture comprising **2**, (±)-**5**, and **8** and observed an ^{1}H NMR spectrum consistent with the formation of a self-sorted mixture of the three homodimeric aggregates **2·2**, (+)-**5**·(−)-**5**, and **8·8** (Figure 9). These results demonstrate that simply by choosing molecular clips that possess different geometrical arrangements of their H-bonding arms it is possible to achieve high-fidelity self-sorting even within a complex mixture. We expect that such mutually orthogonal H-bonding modules have broad potential as triggered components of more complex molecular machines.[5,9]

Designed Homochiral Dimerization and a Second Three-Component Self-Sorting System. Given our success in the preparation of a three-component self-sorting system based on **2·2**, (+)-**5**·(−)-**5**, and **8·8**, we wondered whether we could expand the scope of the system even further. For this purpose we designed (±)-**7**, which is a hybrid molecule whose halves resemble **2** and **8**, respectively. Before synthesizing (±)-**7**, we examined CPK models of **7·7** which suggested that a skewed geometry—similar to **8·8**—based on homochiral dimerization would retain $\pi-\pi$ interactions and maximize the number of H-bonding interactions. This prediction is borne out by experiment. The ^{1}H NMR spectrum of (±)-**7** in $CDCl_3$ shows two sets of resonances corresponding to a clear dimeric aggregate (Figure 10a). As predicted on the basis of CPK models, the X-ray structure reveals that a racemic mixture of homochiral homodimers (+)-**7**·(+)-**7** and (−)-**7**·(−)-**7** (Figure 7b) is formed and adopts a skewed orientation to maximize the $\pi-\pi$ interactions and form four H-bonds.

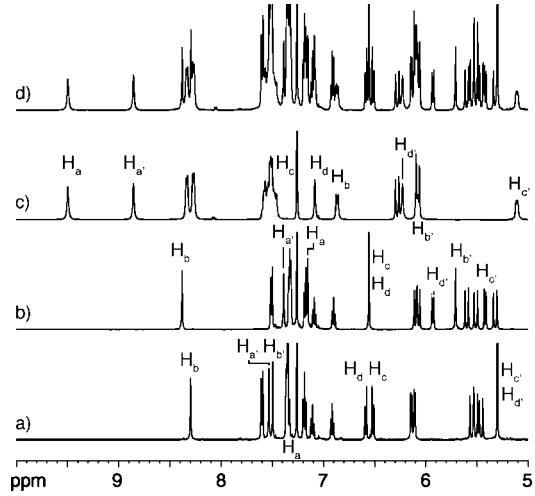


FIGURE 9. ^{1}H NMR spectra (500 MHz, 298 K) for (a) **2·2**, (b) (+)-**5**·(−)-**5**, (c) **8·8**, and (d) a mixture of **2·2**, (+)-**5**·(−)-**5**, and **8·8**.

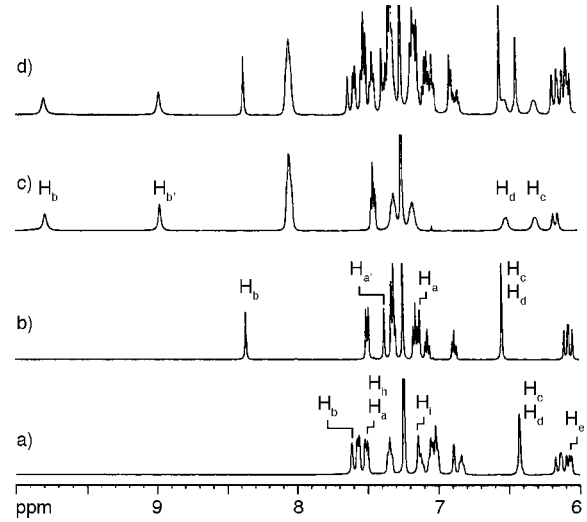


FIGURE 10. ^{1}H NMR spectra (500 MHz, 298 K) for (a) (+)-**7**·(+)-**7**, (b) (+)-**5**·(−)-**5**, (c) **1·1**, and (d) a mixture of **1·1**, (+)-**5**·(−)-**5**, and (+)-**7**·(+)-**7**.

Inspired by the highly enantioseletive recognition behavior imprinted in the chiral backbone of (±)-**7**, we decided to study the behavior of this new molecular clip in the presence of other molecular clips. We prepared various binary mixtures of (±)-**7** with achiral and chiral molecular clips and observed the outcome of the resulting mixture by ^{1}H NMR spectroscopy. When we mixed equimolar amounts of (±)-**7** and achiral **1** or **2**, we found that they form a binary self-sorting mixture comprising (+)-**7**·(+)-**7** and (−)-**7**·(−)-**7**, and **1·1** or **2·2**. This result demonstrates that the cleft of chiral (±)-**7** is not complementary to either **1** or **2**, due to a geometric mismatch between their H-bonding arms. Similarly, in an equimolar mixture of (±)-**7** with (±)-**4a** or (±)-**5**, we observed the coexistence of homochiral ((+)-**7**·(+)-**7** and (−)-**7**·(−)-**7**) and heterochiral ((+)-**4a**·(−)-**4a** or (+)-**5**·(−)-**5**) dimeric molecular clips—a result

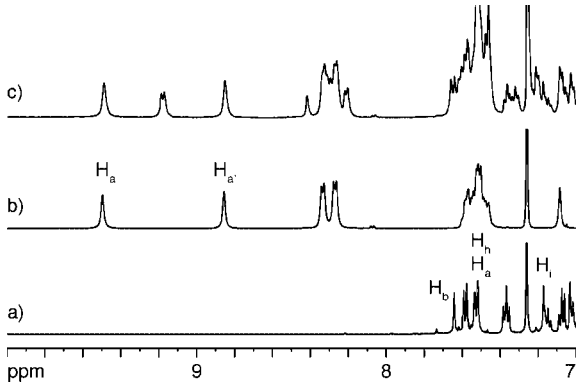


FIGURE 11. Portiona of the ^{1}H NMR (1 mM, 500 MHz, $CDCl_3$, room temperature) spectra recorded for (a) a racemic mixture of (+)-**7**·(+)-**7** and (−)-**7**·(−)-**7**, (b) **8**·**8**, and (c) a mixture of (+)-**7**·(+)-**7** and (−)-**7**·(−)-**7**, **8**·**8**, (+)-**7**·**8**, and (−)-**7**·**8**.

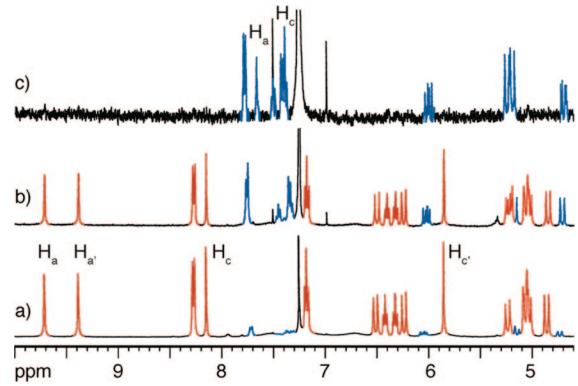


FIGURE 12. Portions of the ^{1}H NMR spectra recorded for **9**·**9** (400 MHz, $CDCl_3$, room temperature) upon dilution: (a) 11 mM; (b) 1.1 mM; (c) 0.11 mM. Resonances are color-coded as follows: dimeric **9**·**9**, red; monomeric **9**, blue.

that demonstrates self-sorting based on chirality (Supporting Information). In accord with these observations, when we mixed **1**, (±)-**5**, and (±)-**7** we observed an NMR spectrum that was the sum of those measured for **1**·**1**, heterochiral (+)-**5**·(−)-**5**, and a racemic mixture of homochiral (+)-**7**·(+)-**7** and (−)-**7**·(−)-**7** dimers (Figure 10), which indicates a high-fidelity self-sorting event.

Although we were delighted to observe such high levels of homochiral and heterochiral recognition within the three-component self-sorting systems, we wanted to extend the system toward larger numbers of simultaneously self-sorting molecular clips. When an equimolar mixture of (±)-**7** and **8** was prepared, we observed a mixture of homodimers and heterodimers by ^{1}H NMR (Figure 11). The lack of self-selectivity in mixture of (±)-**7** and **8** can be rationalized from their X-ray crystal structures. Both molecular clips form dimeric aggregates in which the opposing clips are skewed with respect to each other. Similarities in the spatial distribution of the H-bonding arm of molecular clips (±)-**7** and **8** reduce their ability to discriminate between self and nonself within this binary mixture.

Selective Dissociation of One Member of a Self-Sorted Mixture. The heterodimerization of (±)-**7** and **8** was disappointing, in that we were precluded from preparing a four-component self-sorting system comprising **2**, **5**, (±)-**7**, and **8**. When considered from a different viewpoint, it enables a useful type of stimuli responsiveness that will be particularly useful in the engineering of complex and functional chemical systems. Consider, for example, a system comprising four members (A−D). Of the 10 homodimeric and heterodimeric species (AA, BB, CC, DD, AB, AC, AD, BC, BD, CD) that would comprise an unbiased dynamic combinatorial library, a high-fidelity self-sorting system is only able to access the four homodimeric states (e.g., AA, BB, CC, DD). The ability to selectively access heterodimeric states (e.g., BD) by suitable chemical stimuli (e.g., addition of molecular clip D) would allow fine tuning of the topology of the interaction network that characterizes this four-component mixture.[16] In this context, we examined the addition of a fourth component to pre-existing three-component self-sorting systems. As expected, addition of a racemic mixture of (+)-**7**·(+)-**7** and (−)-**7**·(−)-**7** to a self-sorted mixture comprising **2**·**2**, (+)-**5**·(−)-**5**, and **8**·**8** results in the selective heterodimerization of **8**·**8** under the formation of (±)-**7**·**8** (Figure S13, Supporting Information). Similarly, the addition of **1**·**1** to a self-sorting mixture comprising **2**·**2**, (+)-**5**·(−)-**5**, and **8**·**8** results in the selective heterodimerization of **2**·**2** under the formation of **1**·**2** (Figure S14, Supporting Information). We envision that the ability to selectively alter the interaction network of one component (or one subset of components) of a complex self-sorting mixture by addition of a new component will enable the construction of functional stimuli responsive systems.

Steric Effects Influence the Thermodynamics and Kinetics of Dimerization. In the next phase of our search for self-sorting systems comprising larger numbers of molecular clips, we decided to introduce steric congestion onto the *o*-xylylene sidewalls. We hypothesized that increased steric interactions between two molecular clips would destabilize their homodimers more dramatically than their heterodimers. This hypothesis is supported by simulations reported previously[14] which show that the system comprising *one* tight and *one* weak homodimer is thermodynamically more favorable than the alternative arrangement featuring *two* heterodimers of modest strength. Therefore, we anticipated that a mixture of two homodimers—one sterically hindered and one unsubstituted—might constitute a self-sorting system.

We choose compound **8** as the base system—because it forms a tight dimer and we thought it would be straightforward to modify synthetically—and gradually increased the number of substituents in order to test the influence of steric congestion on dimeric aggregation. Accordingly, we prepared tetramethyl benzanilide (**9**) and tetramethyl pivalanilide (**10**). When a 2.5 mM solution of **9** in $CDCl_3$ was examined by ^{1}H NMR spectroscopy at room temperature, we observed two sets of peaks. After warming the same solution gradually to 55 °C, we observed a decrease in the intensity of one set of peaks concomitant with an increase in the intensity of the other set (Supporting Information). An indistinguishable spectrum was obtained when this solution was cooled slowly to room temperature. A similar change in the system was observed when an 11 mM solution of **9**·**9** was diluted 100-fold to 0.11 mM (Figure 12). These observations suggest that **9** exists in equilibrium with **9**·**9** with slow exchange kinetics relative to the chemical shift time scale at room temperature. Apparently, steric interactions between the methyl substituents on the aromatic walls of **9**·**9** thermodynamically destabilize the dimer. Interestingly, however, the kinetics of exchange (e.g., k_{off}) remain slow (as observed for **8**·**8**) even as K_a is decreased. Conveniently, the observed slow exchange between monomer and dimer on the chemical shift time scale allows us to follow this equilibrium by ^{1}H NMR spectroscopy and calculate the

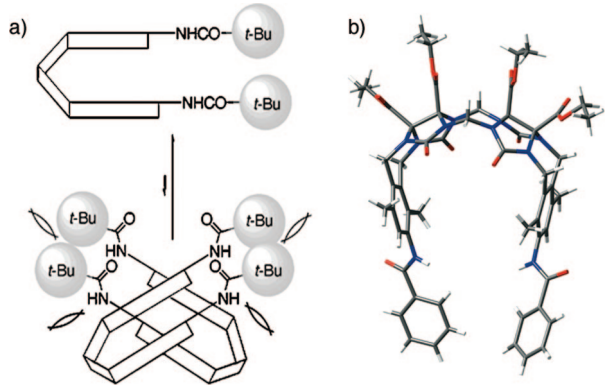


FIGURE 13. Molecular clips that remain monomeric in solution: (a) steric bulk preventing dimeric aggregation of **10**; (b) crystal structure of (±)-**12** showing the display of H-bonding groups in front of the cleft, which leads to steric hindrance to dimerization.

association constant by measuring the integrals for monomer versus dimer at various concentrations (K_s = 2900 ± 600 mol^{-1}). We incorporated additional steric congestion in **10** in the form of *t*-Bu(C═O)NH− H-bonding arms (Figure 13a). In this case, the chemical shifts of the aromatic as well as the amide protons do not change in the dilution experiment, which suggests that **10** exists as a monomer (Supporting Information). Interestingly, when we constructed an equimolar binary mixture of **10** and **9**, an NMR spectrum was a superposition of the spectra of the components. The presence of severe steric congestion around the cleft of the hypothetical homodimer **10·10** and heterodimer (±)-**9·10** dictates that compound **10** must remain monomeric (Supporting Information).

As described earlier, the relative orientation of H-bonding sidearms in C_s- or C_2-symmetrical molecular clips (e.g., *parallel* in **1** and **2** versus *antiparallel* in (±)-**4a** and (±)-**5**) endow them with the ability to efficiently distinguish between self versus nonself. Accordingly, we prepared (±)-**11** and (±)-**12**, which are the C_2-symmetric regioisomers of C_s-symmetric **8** and **9**. Interestingly, although not unexpectedly, we did not find any evidence of discrete dimer formation in the ^{1}H NMR spectra of (±)-**11** and (±)-**12**. In the molecular structures of (±)-**11** and (±)-**12** the H-bonding pendant arms are displayed in divergent directions on the tips of the aromatic rings and, therefore, block the face of the cleft, create steric hindrance to dimerization, and prevent association with a second molecular clip. The molecular clips (±)-**11** and (±)-**12** do not form well-defined discrete dimers such as those formed by **8** or **9**. Rather, we observe broadening and upfield shifting in their ^{1}H NMR spectra, which indicates that (±)-**11** and (±)-**12** form poorly structured oligomeric species in solution (Supporting Information). The solid-state behavior is similarly affected; unlike **8**, which exists as a dimer, compound (±)-**12** remains monomeric in the crystal (Figure 13b). These results—which show that both $\pi-\pi$ and H-bonds are required to form discrete dimeric aggregates—further validate the use of molecular clips as a platform for the construction of complex self-sorting systems. For example, the transition from monomer to discrete dimer to poorly defined oligomeric states can be programmed into the system by the identity and spatial orientation of the substituents on the *o*-xylylene sidewalls of the constituent molecular clips.

Effect of Additional H-Bonding Groups on the Ability of Molecular Clips To Undergo Self-Assembly and Self-Sorting. After exploring the influence of geometry, sterics, and chirality on the ability of molecular clips to undergo self-assembly and self-sorting, we decided to investigate the influence of the number and pattern of H-bonding donors and acceptors in the pendant arm on the fidelity of self-sorting. We synthesized **3**, which contains additional $NH(CO)CH_3$ H-bonding groups in the para position of the pendant aromatic rings. We thought that **3** might form a very robust aggregate, due to an increased number of H-bonding interactions upon dimerization. We further predicted that **3** might undergo self-sorting with **1** or **2** on the basis of differences in the number of H-bonds in the aggregate (Figure 14a,b). When **3** was dissolved in $CDCl_3$, we observed upfield shifting, severe broadening, and multiple resonances for some protons, which indicates the formation of multiple ill-defined species in solution. Upon further examination of a CPK model of **3**, we realized that the flexibility of the pendant arm of **3** increases as the arm gets longer. Due to this lack of rigidity, unsatisfied H-bond donors in the amide group farthest from the clip can interact with unsatisfied H-bond acceptors on other molecules of **3** or assemblies of **3**, resulting in uncontrolled higher order aggregation.[24]

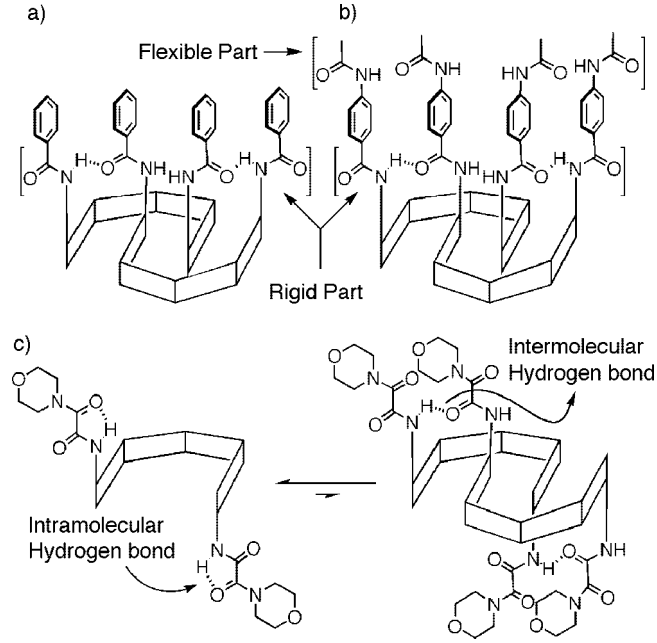


FIGURE 14. Schematic representation of the aggregates formed by (a) **1·1**, (b) **3·3**, and (c) (±)-**6**.

Compounds **2** and (±)-**5** contain an H-bond *donor−acceptor−donor* arrangement in the ureidyl group. We hypothesized that a molecular clip with a specific donor−acceptor arrangement in the pendant H-bonding arms might undergo self-sorting with another clip that possessed a different donor−acceptor arrangement. In order to test that hypothesis, we synthesized compound (±)-**6**, containing H-bonding groups having a *donor−acceptor−acceptor* pattern. When (±)-**6** was dissolved in $CDCl_3$, we observed an upfield shift of the proton attached to its *o*-xylylene sidewall, indicating that (±)-**6** forms an aggregate in solution.

(24) Interestingly, examination of the X-ray crystal structures of **1** and **2** shows that the two internal amide protons remain free in the dimeric aggregate. Upon careful inspection, we conclude that these amide protons are actually involved in weak electrostatic interactions with the ureidyl C═O group and also that they are not accessible to any external H-bond acceptors because they are buried inside the molecular architecture.

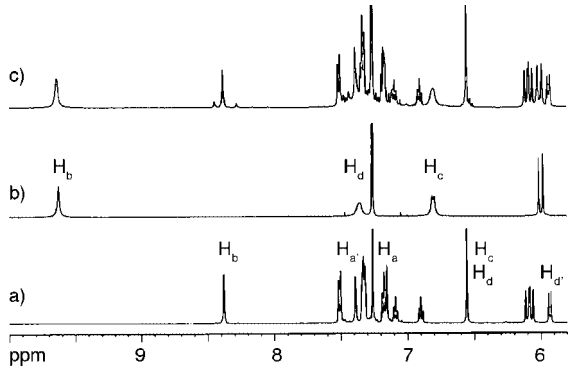


FIGURE 15. Portions of the ^{1}H NMR (2 mM, 500 MHz, $CDCl_3$, room temperatue) spectrum recorded for (a) (+)-**5**·(−)-**5**, (b) (±)-**6**, and (c) a mixture of (+)-**5**·(−)-**5**, and (±)-**6**.

Unlike (+)-**4a**·(−)-**4a** and (+)-**5**·(−)-**5**, we did not observe any doubling of resonances due to aggregation, as the molecule undergoes fast exchange on the chemical shift time scale. Interestingly, when a solution of (±)-**6** was diluted, we observed a downfield shift of the amide protons (Supporting Information). Usually the amide protons move upfield in dilution experiments as the H-bonds are disrupted with increasing dilution. This result indicates the presence of two strong intramolecular H-bonds in monomer (±)-**6** which are sacrificed to form two weak intermolecular H-bonds and $\pi-\pi$ interactions during dimerization. Accordingly, compound (±)-**6** forms a weak dimer (K_s = 17.5 ± 2.2 mol^{-1}) in $CDCl_3$ solution (Figure 14c). When we mixed (±)-**6** with an equimolar amount of (±)-**5**, we mainly observed the separate coexistence of (±)-**6** and (+)-**5**·(−)-**5** in the solution with a very small amount of heteromeric assemblies (Figure 15). This observation suggests that the tendency of molecular clips with a common geometrical arrangement of their H-bonding arms toward formation of mixtures of homo- and heterodimers can be suppressed with concomitant enhancement of self-selectivity by incorporating an electronic mismatch between their H-bonding arms.

Four-Component Self-Sorting System. If we consider that only monomeric and dimeric aggregates can exist in solution, then a mixture of 4 molecular clips (A−D) can give rise to 14 different species (A, B, C, D, A_2-D_2, AB, AC, AD, BC, BD, CD). In our quest for a four-component self-sorting system—for use as orthogonal supramolecular modules for studies of systems chemistry—we screened a large number of different combinations guided by the principles discussed above. Initially, we examined an equimolar mixture of **2**, (±)-**5**, and **9** and observed a self-sorted mixture by ^{1}H NMR spectroscopy due to the disparate spatial orientation of their H-bonding arms. On the basis of the fact that **9** and **10** constitute a self-sorting system (vide supra), we decided to prepare a mixture comprising molecular clips **2**, (±)-**5**, **9**, and **10**. Remarkably, this set of 4 molecular clips exists in a self-sorted state (Figure 16) comprising 5 different species—**2**·**2**, (+)-**5**·(−)-**5**, **9** in equilibrium with **9**·**9**, and monomeric **10**—out of 14 possibilities.

Conclusions

In summary, we presented the synthesis of methylene-bridged glycoluril dimers **1**−**12**, which undergo strong dimerization in $CDCl_3$ due to a combination of H-bonding and $\pi-\pi$ interactions. The structure of these dimeric aggregates changes as the position and relative orientation of the two H-bonding groups move around the *o*-xylylene rings. For example, **1**·**1** and **2**·**2** form homodimers and (+)-**4a**·(−)-**4a** and (+)-**5**·(−)-**5** undergo heterochiral recognition, both with an in register type geometry. When H-bonding groups were moved to the tips of the aromatic rings (e.g., **8**·**8** and **9**·**9**), a skewed geometry was observed that maximizes H-bonding and $\pi-\pi$ interactions. Most interesting is (±)-**7**, which forms the homochiral homodimers (+)-**7**·(+)-**7** and (−)-**7**·(−)-**7** based on a skewed geometry. Steric bulkiness around the cleft of these molecular clips (e.g., **9** and **10**) leads to reduced values of K_a, but slow exchange kinetics relative to the ^{1}H NMR time scale are maintained. The high levels of self-selectivity of these molecular clips allowed us to prepare three-component (**2**, (±)-**5**, and **8**; **1**, (±)-**5**, and (±)-**7**) and even a four-component self-sorted system (**2**, (±)-**5**, **9**, and **10**).

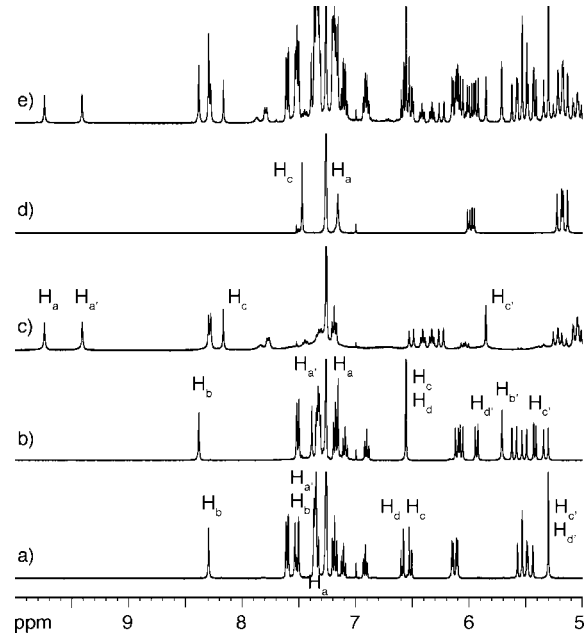


FIGURE 16. ^{1}H NMR spectra (400 MHz, 298 K) for (a) **2**·**2**, (b) (+)-**5**·(−)-**5**, (c) **9**·**9**, (d) **10**, and (e) a mixture of **2**·**2**, (+)-**5**·(−)-**5**, **9**·**9**, and **10**.

The implications of this research go beyond the system-specific considerations described above. The availability of a series of robust, easily functionalized, and orthogonal H-bonding modules for assembly in nonpolar solvents such as $CDCl_3$ can be utilized for numerous applications. For example, the patterning of surfaces using two orthogonal recognition units has recently been demonstrated; additional levels of patterning could be added along with stimuli control based on molecular clips reported herein. Such modules also enable the noncovalent derivatization of polymer backbones in solution to optimize their properties for specific applications (e.g., light emitting diodes, drug delivery, tissue engineering).[3] Although the molecular clips described herein assemble in nonpolar solvents, water-soluble versions of these compounds also assemble in water. When such water-soluble molecular clips also exhibit self-sorting, it would be possible to use them as tags to promote dimerization of appended (bio)molecules within complex cellular environments.

Perhaps most significantly, the development of dynamic combinatorial chemistry and self-sorting systems has helped stimulate the development of systems chemistry. In unbiased dynamic combinatorial libraries all constituent states are equally populated and application of a chemical stimulus leads to enhanced formation of one or more members of the library due

to favorable noncovalent interactions. Similar to natural systems—whose noncovalent interaction networks are tightly controlled—self-sorting systems typically comprise only a small fraction of the conceivable noncovalent aggregates. In this paper, we demonstrated that the addition of a new molecular clip (e.g., **1**) to a self-sorting mixture (e.g., **2·2**, (+)-**5·**(−)-**5**, and **8·8**) results in the selective heterodimerization of only one member of the system. By extension, it should be possible to prepare larger systems comprising sets of molecular clips with common spatial distribution of their H-bonding arms (e.g., **1**−**3**, **4**−**6**, and **8**−**10**) that display self-sorting between sets but not within sets. The development of stimuli responsive versions of such self-sorting systems—that result in new connection between sets—promises the development of complex systems that exhibit behaviors typically reserved for natural systems.

Experimental Section

General experimental details have been reported previously.[14]

NMR Experiments. NMR spectra were measured on spectrometers operating at 400 or 500 MHz for ^{1}H and 100 or 125 MHz for ^{13}C. Temperature was maintained (±0.5 K) with a temperature control module that has been calibrated using the separation of the resonances of methanol. For the self-association measurements, spectra were recorded at a series of concentrations (10−0.05 mM). Spectra for dimeric clips at higher than 10 mM concentration were recorded in 12 mm microtubes matched with $CDCl_3$. Spectra were referenced relative to residual solvent resonances.

X-ray Crystal Structures for 2·2, (+)-5·(−)-5, (+)-7·(+)-7, 8·8, and 12. Descriptions of the data collection, solution, and refinement of these structures can be found in the Supporting Information. The crystal structures of **1·1** and (+)-**4a·**(−)-**4a** have been reported previously[13] and deposited with the Cambridge Crystallographic Data Center (Nos. CCDC-187956 and CCDC-187957).

Acknowledgment. We thank the National Science Foundation (Grant No. CHE-0615049) and the National Institutes of Health (Grant No. GM61854) for financial support of this work.

Supporting Information Available: Text, tables, and figures giving synthetic procedures and characterization data, selected ^{1}H NMR spectra, ^{1}H and ^{13}C NMR spectra for all new compounds and details of the X-ray structures of **2·2**, (+)-**5·**(−)-**5**, (+)-**7·**(+)-**7**, **8·8**, and (±)-**12**; X-ray data are also given as CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8009424