VOLUME 69, NUMBER 19 JOC Articles SEPTEMBER 17, 2004

Social Self-Sorting in Aqueous Solution

Pritam Mukhopadhyay,[†] Anxin Wu,[†,‡] and Lyle Isaacs*,[†]

Department of Chemistry and Biochemistry, University of Maryland, College Park, Maryland 20742, and
College of Chemistry, Central China Normal University,
Wuhan, Hubei 430079, People's Republic of China

lisaacs@umd.edu

Received January 2, 2004

Self-sorting—the ability to efficiently distinguish between self and nonself—is common in nature but is still relatively rare in synthetic supramolecular systems. We report a 12-component mixture comprising **1**−**11** and KCl that undergoes thermodynamically controlled self-sorting in aqueous solution based on metal−ligand, ion−dipole, electrostatic, charge-transfer interactions, as well as the hydrophobic effect. We refer to this molecular ensemble—characterized by high-fidelity host−guest interactions between components—as a social self-sorting system to distinguish it from narcissistic self-sorting systems based on self-association processes. The influence of several key variables—temperature, pH, concentration, and host/guest stoichiometry—was explored by a combination of simulation and experiment. Variable temperature NMR experiments, for example, revealed a kinetically controlled irreversible process upon cycling from 298 to 338 K, which is an emergent property of this molecular ensemble. Variable pH and concentration experiments, in contrast, did not reveal any emergent properties of the molecular ensemble. Simulations of a four-component mixture establish that by proper control of the relative magnitude of the various equilibrium constants, it is possible to prepare socially self-sorted mixtures that are responsive (irresponsive) to host/guest stoichiometry over narrow (broad) ranges. The 12-component mixture is relatively irresponsive to host/guest stoichiometry. Such social self-sorting systems, like their natural counterparts, have potential applications as chemical sensors, as artificial regulatory elements, and in the preparation of biomimetic systems.

Introduction

Self-sorting−the ability to efficiently distinguish between self and nonself within complex mixtures−is a fundamental property of natural and biological systems but one that has been less commonly observed in synthetic supramolecular systems. Consider, for example, that fish tend to form schools with members of their own species, that humans form clubs based on common interests, that some compounds undergo spontaneous resolution upon crystallization to form conglomerates,[1] that immiscible liquids undergo phase separation to form biphasic and multi-phasic mixtures,[2] and that small molecules, proteins, and DNA all seek out specific partners in high-fidelity recognition processes.[3] In biology, these complex self-sorting systems are capable of responding to stimuli from their environment, exhibit adaptive behavior, and are capable of evolution. As an initial step toward the preparation of designed molecular systems that exhibit some of the complexity of their natural counterparts, we have been investigating the preparation of complex mixtures of compounds that undergo self-sorting.

Self-sorting systems can be prepared by thermodynamically or kinetically controlled recognition processes. To date, thermodynamically controlled self-sorting processes have been based on the formation of hydrogen bonds,[4−6] metal−ligand interactions,[7,8] solvophobic ef-

---

* To whom correspondence should be addressed. Phone: (301) 405-1884. Fax: (301) 314-9121.

[†] University of Maryland.

[‡] Central China Normal University.

(1) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994.

(2) Hildebrand, J. H. *J. Phys. Colloid Chem.* **1949**, *53*, 944−947.

(3) Stryer, L. *Biochemistry*; 4th ed.; W. H. Freeman: New York, 1995.

(4) Jolliffe, K. A.; Timmerman, P.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 933−937; Cai, M.; Shi, X.; Sidorov, V.; Fabris, D.; Lam, Y.-F.; Davis, J. T. *Tetrahedron* **2002**, *58*, 661−671; 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; Ma, Y.; Kolotuchin, S. V.; Zimmerman, S. C. *J. Am. Chem. Soc.* **2002**, *124*, 13757−13769.

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

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

10.1021/jo049976a CCC: $27.50 © 2004 American Chemical Society
Published on Web 03/06/2004

fects,[9,10] and reversible covalent bonds.[11] We regard heterochiral aggregation[5,12] and enantiomeric self-recognition[13,14] as special cases of self-sorting. Kinetically controlled self-sorting processes based on noncovalent interactions[15] are much less common than those based on covalent bond formation. Particularly elegant examples include kinetic resolutions,[16] target-assisted combinatorial synthesis,[17] self-replication,[18] and chiral selection in template driven nucleic acid oligomerization.[19] Each of these self-sorting processes can occur by either homomeric or heteromeric recognition processes. In homomeric recognition (self-association) processes, molecules display a high affinity for themselves; such processes are commonly referred to as narcissistic self-sorting.[8] In heteromeric recognition (host−guest) processes, molecules display a high affinity for specific other members of the mixture; we have suggested they be described as social self-sorting processes.[6] Among the reported examples of designed synthetic systems that undergo thermodynamic self-sorting, the vast majority fall into the category of narcissistic rather than social self-sorting.[10]

Previously, we questioned whether self-sorting is exceptional behavior or whether it is likely to become a commonly observed phenomenon in molecular recognition and self-assembly.[6] We demonstrated that the preparation of an eight-component narcissistic self-sorting mixture in $CDCl_3$ solution was as simple as selecting the monomeric units from a series of well-defined aggregates from the literature. In $CDCl_3$ solution, the fidelity of self-sorting was controlled by the pattern of H-bonding groups, their spatial orientation, and the presence of a closed network of H-bonds. The generality of this approach toward the preparation of complex self-sorting systems in water was questionable because two of the main driving forces for molecular aggregation in water−electrostatic interactions and the hydrophobic effect−tend to be far less directional than H-bonds. This paper extends our previous work by demonstrating that the preparation of complex self-sorting systems is straightforward even in water and demonstrating the concept of a social self-sorting system.

Results and Discussion

Selection of Molecular Components. Chart 1 shows the chemical structures of the compounds used in this paper (**1**−**11**). We selected 12 components (**1**−**11** and KCl) that are well-known from the literature to generate stable host−guest complexes in aqueous solution. For example, cryptand **1** is well-known to bind to potassium ion.[20] Facially amphiphilic methylene bridged glycoluril dimer **2** undergoes self-association in water to form the dimer **2**$_2$ whereas (±)-**9** undergoes an enantiomeric self-recognition process triggered by the addition of **10**.[14,21] Cucurbit[6]uril (**6**) binds tightly to hexanediammonium ion **3**[22] by a combination of ion−dipole interactions and the hydrophobic effect, whereas cucurbit[8]uril (**8**) promotes the formation of a charge-transfer complex between **4** and **5**.[23] As our final host−guest pair, we selected β-cyclodextrin (**7**) and adamantane carboxylic acid **11**.[24] We selected complexes that met as many of the following criteria as possible: (1) high stability (e.g., $K_a > 10^4$ M^{-1}) in neutral water, (2) large complexation induced changes in chemical shift, and (3) slow exchange between bound

---

(7) Krämer, R.; Lehn, J.-M.; Marquis-Rigault, A. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 5394−5398; Caulder, D. L.; Raymond, K. N. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1440−1442; Enemark, E. J.; Stack, T. D. P. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 932−935; Stiller, R.; Lehn, J.-M. *Eur. J. Inorg. Chem.* **1998**, 977−982; Albrecht, M.; Schneider, M.; Röttele, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 557−559.

(8) Taylor, P. N.; Anderson, H. L. *J. Am. Chem. Soc.* **1999**, *121*, 11538−11545.

(9) Bilgiçer, B.; Xing, X.; Kumar, K. *J. Am. Chem. Soc.* **2001**, *123*, 11815−11816; Bilgiçer, B.; Kumar, K. *Tetrahedron* **2002**, *58*, 4105−4112.

(10) Schnarr, N. A.; Kennan, A. J. *J. Am. Chem. Soc.* **2003**, *125*, 667−671; Schnarr, N. A.; Kennan, A. J. *J. Am. Chem. Soc.* **2003**, *125*, 6364−6365.

(11) Rowan, S. J.; Hamilton, D. G.; Brady, P. A.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1997**, *119*, 2578−2579; Rowan, S. J.; Reynolds, D. J.; Sanders, J. K. M. *J. Org. Chem.* **1999**, *64*, 5804−5814; Rowan, S. J.; Cantrill, S. J.; Cousins, G. R. L.; Sanders, J. K. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 899−952.

(12) Krishnamurthy, R.; Pitsch, S.; Minton, M.; Miculka, C.; Windhab, N.; Eschenmoser, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1537−1541; Vincent, J.-M.; Philouze, C.; Pianet, I.; Verlhac, J.-B. *Chem.—Eur. J.* **2000**, *6*, 3595−3599; Kim, T. W.; Lah, M. S.; Hong, J.-I. *Chem. Commun.* **2001**, 743−744; Oliver, S. R. J.; Clark, T. D.; Bowden, N.; Whitesides, G. M. *J. Am. Chem. Soc.* **2001**, *123*, 8119−8120; Gut, D.; Rudi, A.; Kopilov, J.; Goldberg, I.; Kol, M. *J. Am. Chem. Soc.* **2002**, *124*, 5449−5456; Claessens, C. G.; Torres, T. *J. Am. Chem. Soc.* **2002**, *124*, 14522−14523.

(13) Masood, M. A.; Enemark, E. J.; Stack, T. D. P. *Angew. Chem., Int. Ed.* **1998**, *37*, 928−932; Prins, L. J.; Huskens, J.; de Jong, F.; Timmerman, P.; Reinhoudt, D. N. *Nature* **1999**, *398*, 498−502; Shi, X.; Fettinger, J. C.; Cai, M.; Davis, J. T. *Angew. Chem., Int. Ed.* **2000**, *39*, 3124−3127; Shi, X.; Fettinger, J. C.; Davis, J. T. *J. Am. Chem. Soc.* **2001**, *123*, 6738−6739; Murguly, E.; McDonald, R.; Branda, N. R. *Org. Lett.* **2000**, *2*, 3169−3172; Cooks, R. G.; Zhang, D.; Koch, K. J.; Gozzo, F. C.; Eberlin, M. N. *Anal. Chem.* **2001**, *73*, 3646−3655; Amendola, V.; Fabbrizzi, L.; Gianelli, L.; Maggi, C.; Mangano, C.; Pallavicini, P.; Zema, M. *Inorg. Chem.* **2001**, *40*, 3579−3587; Ishida, Y.; Aida, T. *J. Am. Chem. Soc.* **2002**, *124*, 14017−14019; ten Cate, A. T.; Dankers, P. Y. W.; Kooijman, H.; Spek, A. L.; Sijbesma, R. P.; Meijer, E. W. *J. Am. Chem. Soc.* **2003**, *125*, 6860−6861; Weissbuch, I.; Bolbach, G.; Zepik, H.; Shavit, E.; Tang, M.; Frey, J.; Jensen, T. R.; Kjaer, K.; Leiserowitz, L.; Lahav, M. *J. Am. Chem. Soc.* **2002**, *124*, 9093−9104; De Feyter, S.; Gesquiere, A.; Wurst, K.; Amabilino, D. B.; Veciana, J.; De Schryver, F. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 3217−3220; Provent, C.; Rivara-Minten, E.; Hewage, S.; Brunner, G.; Williams, A. F. *Chem. —Eur. J.* **1999**, *5*, 3487−3494; Rowland, J. M.; Olmstead, M. M.; Mascharak, P. K. *Inorg. Chem.* **2002**, *41*, 1545−1549; Telfer, S. G.; Sato, T.; Kuroda, R.; Lefebvre, J.; Leznoff, D. B. *Inorg. Chem.* **2004**, *43*, 421−429.

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

(15) Prins, L. J.; de Jong, F.; Timmerman, P.; Reinhoudt, D. N. *Nature* **2000**, *408*, 181−184; Paraschiv, V.; Crego-Calama, M.; Ishi-i, T.; Padberg, C. J.; Timmerman, P.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **2002**, *124*, 7638−7639.

(16) Kagan, H. B.; Fiard, J. C. *Top. Stereochem.* **1988**, *18*, 249−330.

(17) Giger, T.; Wigger, M.; Audetat, S.; Benner, S. A. *Synlett* **1998**, 688−691; Nicolaou, K. C.; Hughes, R.; Cho, S. K.; Winssinger, N.; Smethurst, C.; Labischinski, H.; Endermann, R. *Angew. Chem., Int. Ed.* **2000**, *39*, 3823−3828; Nguyen, R.; Huc, I. *Angew. Chem., Int. Ed.* **2001**, *40*, 1774−1776; Lewis, W. G.; Green, L. G.; Grynszpan, F.; Radic, Z.; Carlier, P. R.; Taylor, P.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 1053−1057.

(18) Orgel, L. E. *Nature* **1992**, *358*, 203−209; Luther, A.; Brandsch, R.; von Kiedrowski, G. *Nature* **1998**, *396*, 245−248; Wintner, E. A.; Conn, M. M.; Rebek, J., Jr. *Acc. Chem. Res.* **1994**, *27*, 198−203; Saghatelian, A.; Yokobayashi, Y.; Soltani, K.; Ghadiri, M. R. *Nature* **2001**, *409*, 797−801; Paul, N.; Joyce, G. F. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 12733−12740; Issac, R.; Chmielewski, J. *J. Am. Chem. Soc.* **2002**, *124*, 6808−6809.

(19) Joyce, G. F.; Visser, G. M.; van Boeckel, C. A. A.; van Boom, J. H.; Orgel, L. E.; van Westrenen, J. *Nature* **1984**, *310*, 602−604; Bolli, M.; Micura, R.; Eschenmoser, A. *Chem. Biol.* **1997**, *4*, 309−320.

(20) Dietrich, B.; Lehn, J.-M.; Sauvage, J. P. *Tetrahedron Lett.* **1969**, *34*, 2889−2892.

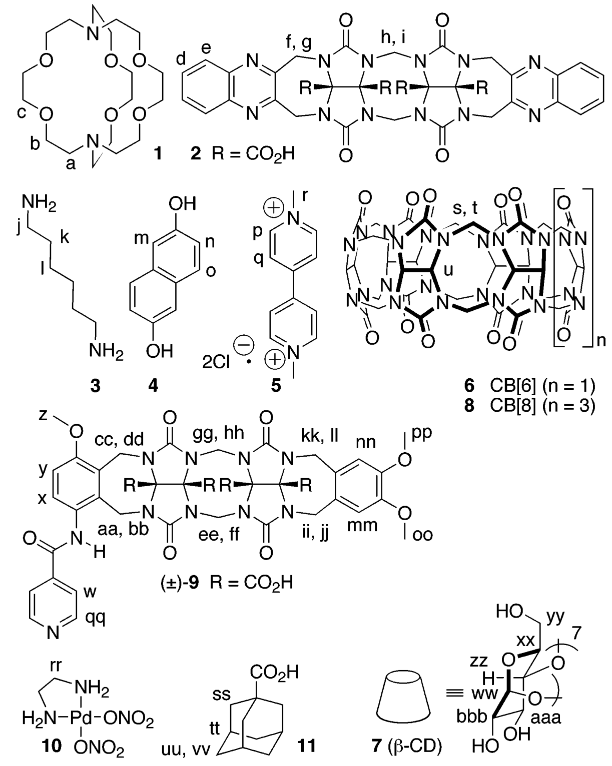
(21) Witt, D.; Lagona, J.; Damkaci, F.; Fettinger, J. C.; Isaacs, L. *Org. Lett.* **2000**, *2*, 755−758.

(22) Mock, W. L.; Shih, N. Y. *J. Org. Chem.* **1986**, *51*, 4440−4446.

(23) Kim, H.-J.; Heo, J.; Jeon, W. S.; Lee, E.; Kim, J.; Sakamoto, S.; Yamaguchi, K.; Kim, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 1526−1529.

(24) Rekharsky, M. V.; Inoue, Y. *Chem. Rev.* **1998**, *98*, 1875−1917.

CHART 1



and free guest on the chemical shift time scale. Most importantly, we chose **1**−**11** so that crossover heteromeric aggregates between the various components were possible (Supporting Information, Figure S1). For example, the cucurbiturils **6** and **8** can form the crossover aggregates **6·5** and **8·3**. Similarly, the possibility existed for crossover aggregation between **2**, (±)-**9**, and **10**. Last, **7** is a notoriously promiscuous host, forming host−guest complexes with many hydrophobic species in water.[24]

12-Component Social Self-Sorting in Water. Figure 1A−F shows the ^{1}H NMR spectra recorded for each of the six selected complexes (**1**·K$^+$, **2**$_2$, **6·3**, **8·4·5**, **9**$_2$·**10**$_2$, and **7·11**). In accord with the literature reports, each of these complexes exhibits a well-defined set of ^{1}H NMR resonances with significant complexation induced changes in chemical shift. Figure 1G shows the ^{1}H NMR spectrum of the mixture of these 12 molecular components. Remarkably, the ^{1}H NMR spectrum of the mixture (Figure 1G) is simply equal to the sum of the NMR spectra of the individual components (Figure 1A−F). This spectroscopic earmark provides strong evidence that the mixture comprising **1**−**6**, **8**−**7**, and KCl undergoes self-sorting. In contrast to self-sorting systems that rely on highly self-selective behavior−narcissistic self-sorting−the self-sorting displayed by the present mixture relies on high affinity of particular host−guest pairs of molecules. To distinguish between the two types of behavior, we refer to the mixture of **1**−**11** and KCl as a social self-sorting system.[6] To demonstrate that the social self-sorting observed in this system is based on thermodynamic rather than kinetic control, we designed an experiment to approach the equilibrium from another direction. We prepared two submixtures (Figure 1H: **2**, **5**−**8**, **10**, and K$^+$ and Figure 1I: **1**, **3**, **4**, (±)-**9**, and **11**) neither of which contain any of the host−guest pairs observed at equilibrium. Hosts **1**, **2**, **6**−**8**, and (±)-**9** are, therefore, forced to socialize with the guests that are present within their respective submixtures. Upon mixing the two submixtures, however, we once again observe a ^{1}H NMR spectrum (Figure 1J) that is simply equal to the sum of the NMR spectra of its components, which establishes that this social self-sorting system is thermodynamically controlled.

Variables that Affect the Fidelity of Social Self-Sorting Processes. As in any molecular recognition or self-assembly study, there are several variables that can affect the outcome of a social self-sorting experiment. In this section, we explore the influence of temperature, pH, concentration, and relative stoichiometry on the behavior of **1**−**11** and KCl by a combination of simulation and experiment.

Temperature. One of the most important variables governing noncovalent interactions in homogeneous solution is temperature. The influence of temperature is particularly important in aqueous solution where values of ΔH, and therefore changes in equilibrium constant, can be large. Figure 2A−G shows the ^{1}H NMR spectrum recorded for the mixture of **1**−**11** and KCl as the temperature is raised from 280 to 338 K. At higher temperatures, new sets of resonances and increased spectral broadening become apparent. In particular, the methylene resonances observed for **6·3** between 0 and 1 ppm, and the aromatic resonances for **8·4·5** and **9**$_2$·**10**$_2$ between 6.2 and 9.5 ppm, become quite complex. In addition to spectral complexity observed at high temperatures (Figure 2G), the system undergoes an irreversible change when the temperature is returned to 291 K (Figure 2H). This irreversible change is an emergent property of the mixture that is not observed for the isolated components. To investigate the origin of this irreversible change, we prepared less complex mixtures comprising 10 (**1**·K$^+$, **2**$_2$, **6·3**, **8·4·5**, and **7·11**) and nine (**1**·K$^+$, **6·3**, **8·4·5**, and **7·11**) components that lack palladium complex **10**, pyridyl ligand (±)-**9**, and quinoxaline **2** (Supporting Information, Figure S2). The 10-component mixture exhibits largely reversible behavior, but small peaks were observed for uncomplexed **5**, which is consistent with the partial dissociation of **8·4·5**.[25] In contrast, the nine-component mixture exhibits completely reversible behavior over the 280−338 K temperature range. On the basis of these control experiments, we hypothesized that the irreversible behavior of the 12-component mixture was due to undesired interactions between **6·3** and **9**$_2$·**10**$_2$, which was confirmed by VT-NMR measurements on this four-component mixture. This thermally induced kinetically irreversible process is one of many emergent processes that may be expected from social self-sorting systems.

Value of pH. The formation of six aggregates from **1**−**11** and KCl is driven by ion−dipole interactions (**1**·K$^+$, **6·3**, and **8·4·5**), metal−ligand interactions (**1**·K$^+$ and **9**$_2$·**10**$_2$), and the hydrophobic effect (**6·3**, **8·4·5**, **2**$_2$, **9**$_2$·**10**$_2$, and **7·11**). Changes in pD that result in changes in the protonation state of the various components have the potential to affect the fidelity of self-sorting (Supporting

---

[25] We have encountered observed difficulties in obtaining quantitative formation of termolecular complex **8·4·5** from its constituents when the conditions vary from the literature report.

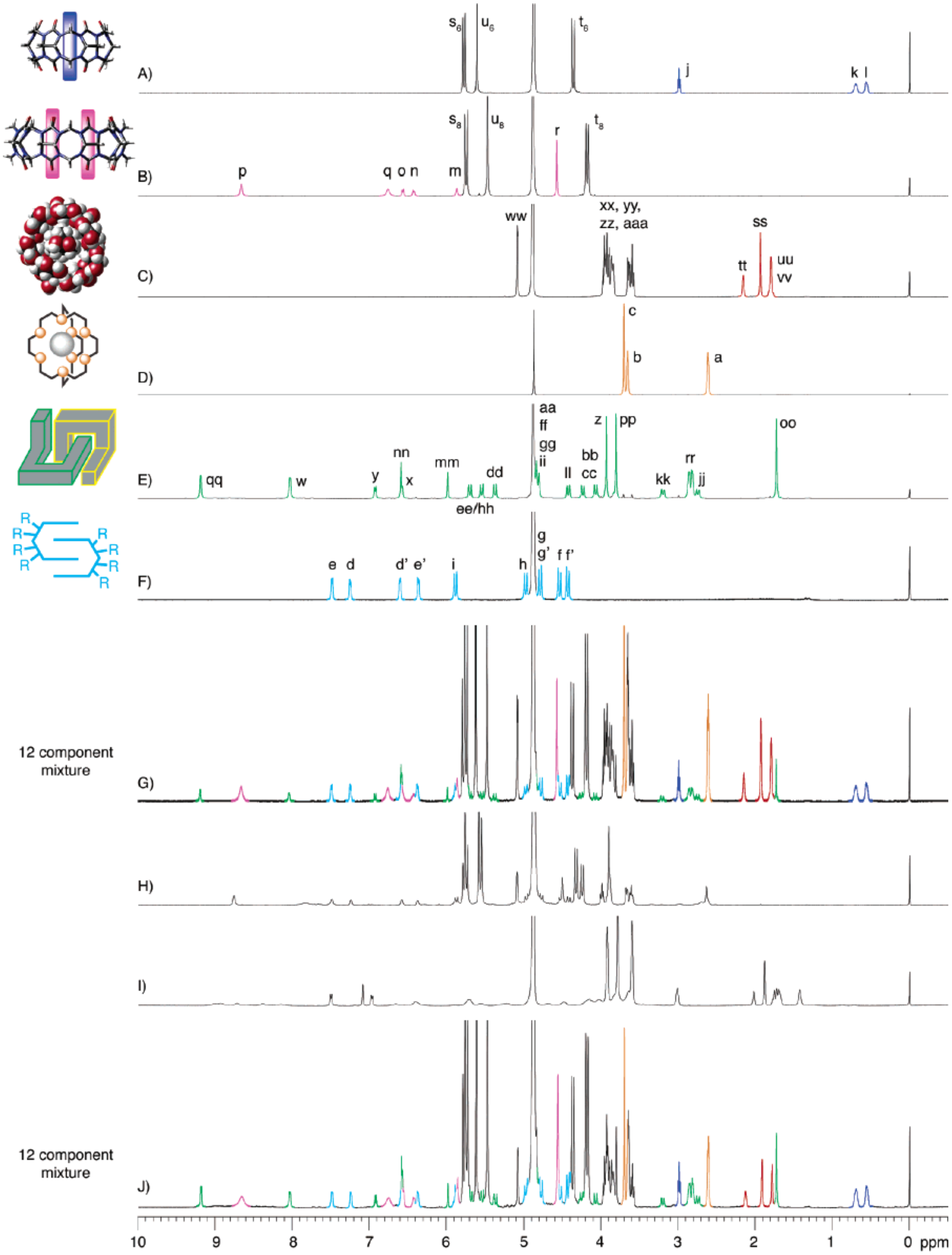


FIGURE 1. ^{1}H NMR spectra (500 MHz, D_2O, pD 7.4, 1.0 mM, 298 K) recorded for (A) $\mathbf{6}\cdot\mathbf{3}$; (B) $\mathbf{8}\cdot\mathbf{4}\cdot\mathbf{5}$; (C) $\mathbf{7}\cdot\mathbf{11}$; (D) $\mathbf{1}\cdot K^+$; (E) $\mathbf{9}_2\cdot\mathbf{10}_2$; (F) $\mathbf{2}_2$; (G) a mixture of **1**−**11** and KCl; (H) a mixture of **2**, **5**−**8**, **10**, and KCl; (I) a mixture **1**, **3**, **4**, (±)-**9**, and **11**; and (J) a mixture of **1**−**11** and KCl prepared by mixing the solutions used to record spectra H and I.

Information, Figure S3). Accordingly, when the self-sorted mixture (pD 7.4) is made alkaline (pD 9.4 and 10.4), the fidelity of several of the complexes is compromised. For example, both $\mathbf{6}\cdot\mathbf{3}$ and $\mathbf{8}\cdot\mathbf{4}\cdot\mathbf{5}$ dissociate at pD 10.4, presumably due to changes in the protonation states of **3** and **4**. In addition, $\mathbf{9}_2\cdot\mathbf{10}_2$ is destroyed at higher pD. Of these three processes, only the formation of $\mathbf{6}\cdot\mathbf{3}$ is a reversible process.[25,26] Upon acidification to pD 3.4, we observe the destruction of $\mathbf{1}\cdot K^+$ and the partial dissociation of $\mathbf{8}\cdot\mathbf{4}\cdot\mathbf{5}$. Upon returning to pD 7.4, the deprotonation of cryptand $\mathbf{1}\cdot H^+$ is a fully reversible process, whereas

---

(26) We have previously found that $\mathbf{9}_2\cdot\mathbf{10}_2$ alone undergoes an irreversible change at high pD with the formation of a gray precipitate.

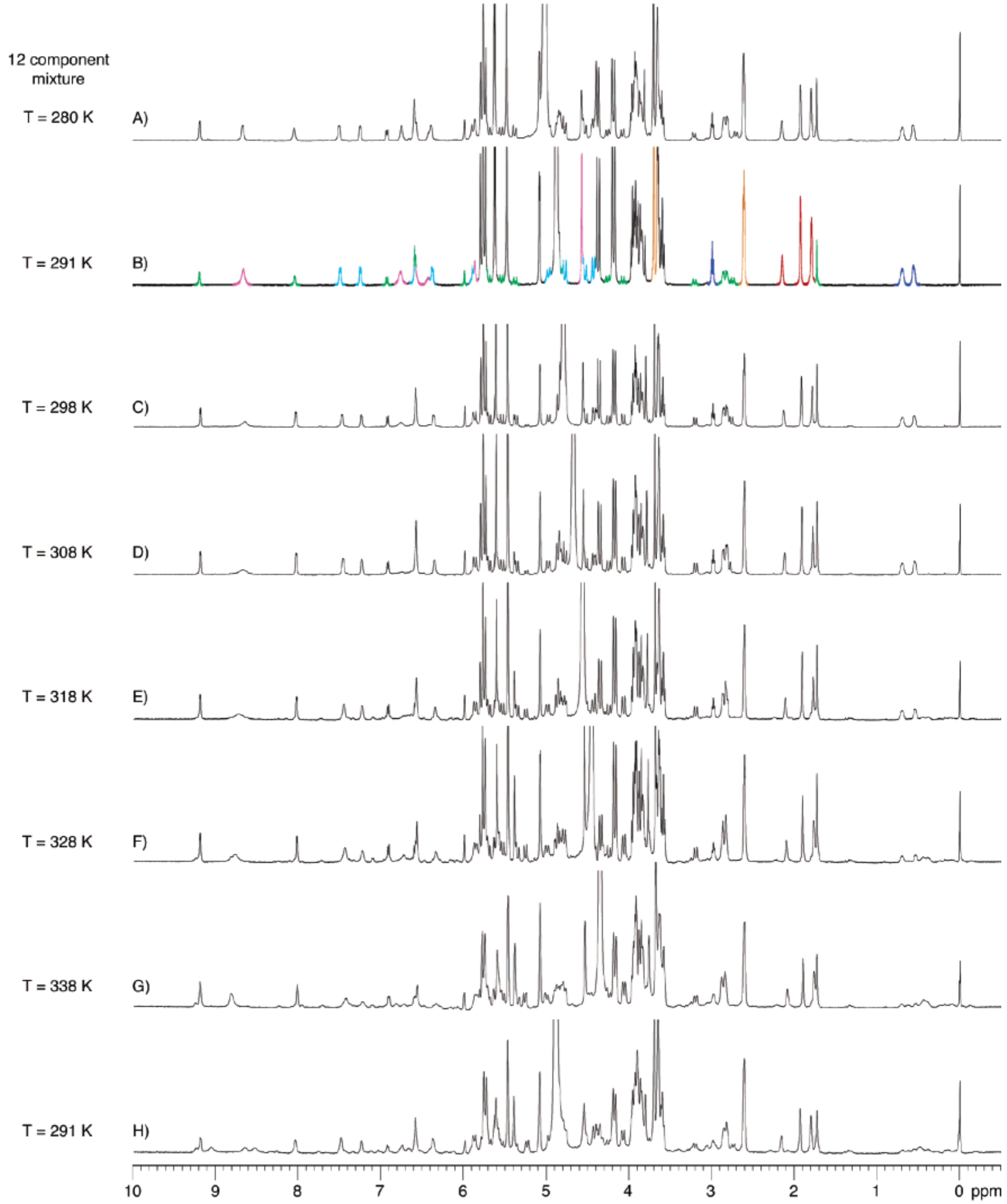


FIGURE 2. Variable temperature ^{1}H NMR spectra (500 MHz, D_2O, pD 7.4, 1 mM) recorded for a mixture of **1**−**11** and KCl at (A) 280 K, (B) 291 K, (C) 298 K, (D) 308 K, (E) 318 K, (F) 328 K, (G) 338 K, and (H) upon cycling from 338 K back to 291 K.

8·4·5 remains partially dissociated. These results highlight the serious difficulties in maintaining a self-sorted system over a wide range of pH; these difficulties are perhaps not surprising when one considers the careful control over pH maintained in biological systems.[3]

Concentration. We wished to quantify the effect of concentration on this social self-sorting system since the dilution of a given host−guest complex (e.g., **8·4·5**) below its value of K_d would result in the release of its guests (e.g., **4** and **5**), which might compete with the formation of other desired host−guest complexes (e.g., $\mathbf{2}_2$ and **6·3**). The ^{1}H NMR spectra obtained upon dilution from 1 mM to 50 μM are given in the Supporting Information (Figure S4). Unlike our previously described eight-component narcissistic self-sorting mixture,[6] this 12-component self-sorted mixture does not respond to dilution over the range of concentration amenable to study by ^{1}H NMR.

Relative Stoichiometry. One of the most important variables in any molecular recognition and self-assembly study is the relative stoichiometry of the various molecular components. Aggregates that are stable at one relative stoichiometry may undergo transformation to a different aggregate at another. How does relative stoichiometry affect the fidelity of social self-sorting? How do the preferences of a set of hosts change as the sea of

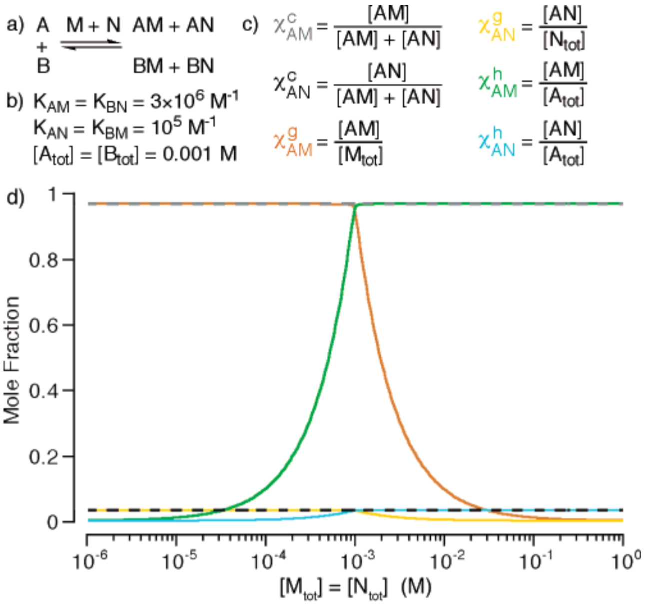


FIGURE 3. Degree of self-sorting in a four-component mixture depends on host−guest stoichiometry: (a) equilibria considered, (b) constraints imposed, (c) mole fraction definitions, and (d) a plot of mole fraction vs guest concentration ($[M_{tot}] = [N_{tot}]$). Legend: χ^{c}_{AM}, gray; χ^{c}_{AN}, black; χ^{g}_{AM}, orange; χ^{g}_{AN}, gold; χ^{h}_{AM}, green; and χ^{h}_{AN}, aqua.

potential guests increases in concentration? The answers to such questions are, of course, determined by the various equilibrium constants and concentrations. We explore two cases by simulation and one by experiment.

Simulation. Consider the simple system described in Figure 3a comprising two hosts (A and B) and two guests (M and N) capable of forming four possible host-guest complexes (AM, AN, BM, and BN).[27] We fix the total concentrations of hosts A and B ($[A_{tot}]$ and $[B_{tot}]$) at 1 mM and choose the four equilibrium constants such that host A has a 30-fold preference for guest M, whereas host B has a 30-fold preference for guest N (Figure 3b). Figure 3d shows a plot of mole fraction versus guest concentration subject to the mole fraction definitions given in Figure 3c. The three sets of related mole fraction definitions with superscripts c, g, and h are referenced to the total concentration of complex, guest, and host, respectively.[28] As the guest concentration is increased from 1 μM to 1 M, the values of χ^{c}_{AM} and χ^{c}_{AN} remain constant. The fidelity of self-sorting remains high when considered from the viewpoint of complexed host molecules. Consider the situation from the point of view, however, of all host molecules (χ^{h}_{AM} and χ^{h}_{AN}). When the guest concentration is low (1−100 μM), relatively few host molecules are complexed, and χ^{h}_{AM} and χ^{h}_{AN} are low. When $[M_{tot}]$ and $[N_{tot}]$ approach $[A_{tot}]$ and $[B_{tot}]$, χ^{h}_{AM} and χ^{h}_{AN} rise and reach their limiting values when the guest/host ratio is greater than unity. Considering the situation from the point of view of the guest leads to the opposite behavior. When $[M_{tot}]$ and $[N_{tot}]$ are less than $[A_{tot}]$ and $[B_{tot}]$, χ^{g}_{AM} and χ^{g}_{AN} are at their maximal values; when the guest/host ratio is greater than unity, the values of χ^{g}_{AM} and χ^{g}_{AN} rapidly decrease. What are the consequences for social self-sorting systems? First, social self-sorting systems are mutually most efficient when the concentrations of the components of each host−guest pair are equal. Second, if each host has highest affinity for a unique guest (e.g., $K_{AM} \gg K_{AN}$ and $K_{BN} \gg K_{BM}$), then the fidelity of self-sorting will not be affected by the total guest concentration as long as $[M_{tot}] = [N_{tot}]$.

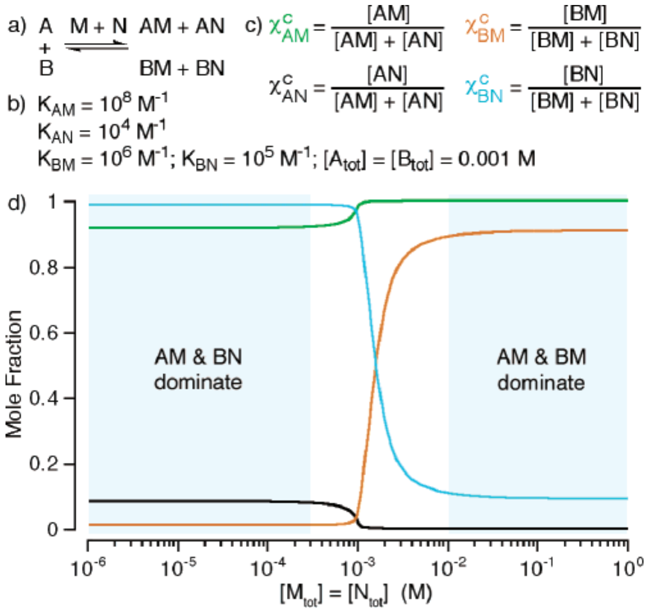


FIGURE 4. Stoichiometry induced partner displacement in a four-component mixture: (a) equilibria considered, (b) constraints imposed, (c) mole fraction definitions, and (d) a plot of mole fraction vs guest concentration ($[M_{tot}] = [N_{tot}]$). Legend: χ^{c}_{AM}, green; χ^{c}_{AN}, black; χ^{c}_{BM}, orange; and χ^{c}_{BN}, aqua.

In the previous example, each host displayed highest affinity for a unique member of the mixture resulting in high fidelity self-sorting over the entire range of relative stoichiometries. What happens if both hosts display highest affinity for the same member of the mixture? Consider the simple four-component system described in Figure 4a subject to the constraints outlined in Figure 4b. We selected the four equilibrium constants such that $K_{AM} \gg K_{AN}$ and $K_{BM} > K_{BN}$. A plot of mole fraction (Figure 4c) versus guest concentration ($[M_{tot}] = [N_{tot}]$) is shown in Figure 4d. At substoichiometric guest concentrations (1 μM to 1 mM), host A selectively binds guest M because K_{AM} is 10^{4}-fold larger than K_{AN}. Host B is forced to socialize with guest N even though K_{BM} is 10-fold greater than K_{BN} because the 10^{4}-fold difference between K_{AM} and K_{AN} is sufficient to overcome the 10-fold driving force favoring BM.[29] When the guest concentration is less than the host concentration, AM and BN are dominant. Conversely, when $[M_{tot}] = [N_{tot}]$ is 2-fold greater than $[A_{tot}] = [B_{tot}]$, there is no scarcity of guest, and each host is free to select its desired partner. Host A selects guest

---

(27) We have neglected the potential interaction of host with host, guest with guest, and higher order aggregates. Such an assumption is likely valid for a system in aqueous solution comprising modestly sized macrocyclic hosts and small guests.

(28) We do not plot the related χ^{c}_{BM}, χ^{c}_{BN}, χ^{g}_{BM}, χ^{g}_{BN}, χ^{h}_{BM}, and χ^{h}_{BN} since they are identical to χ^{c}_{AN}, χ^{c}_{AM}, χ^{g}_{AN}, χ^{g}_{AM}, χ^{h}_{AN}, and χ^{h}_{AM} under the constraints employed.

(29) Perhaps more intuitively, consider the situation from the point of view of guests M and N. Guest M prefers to bind to host A because K_{AM} is 100-fold greater than K_{BM}. Similarly, guest N prefers to bind to host B because K_{BN} is 10-fold greater than K_{AN}.

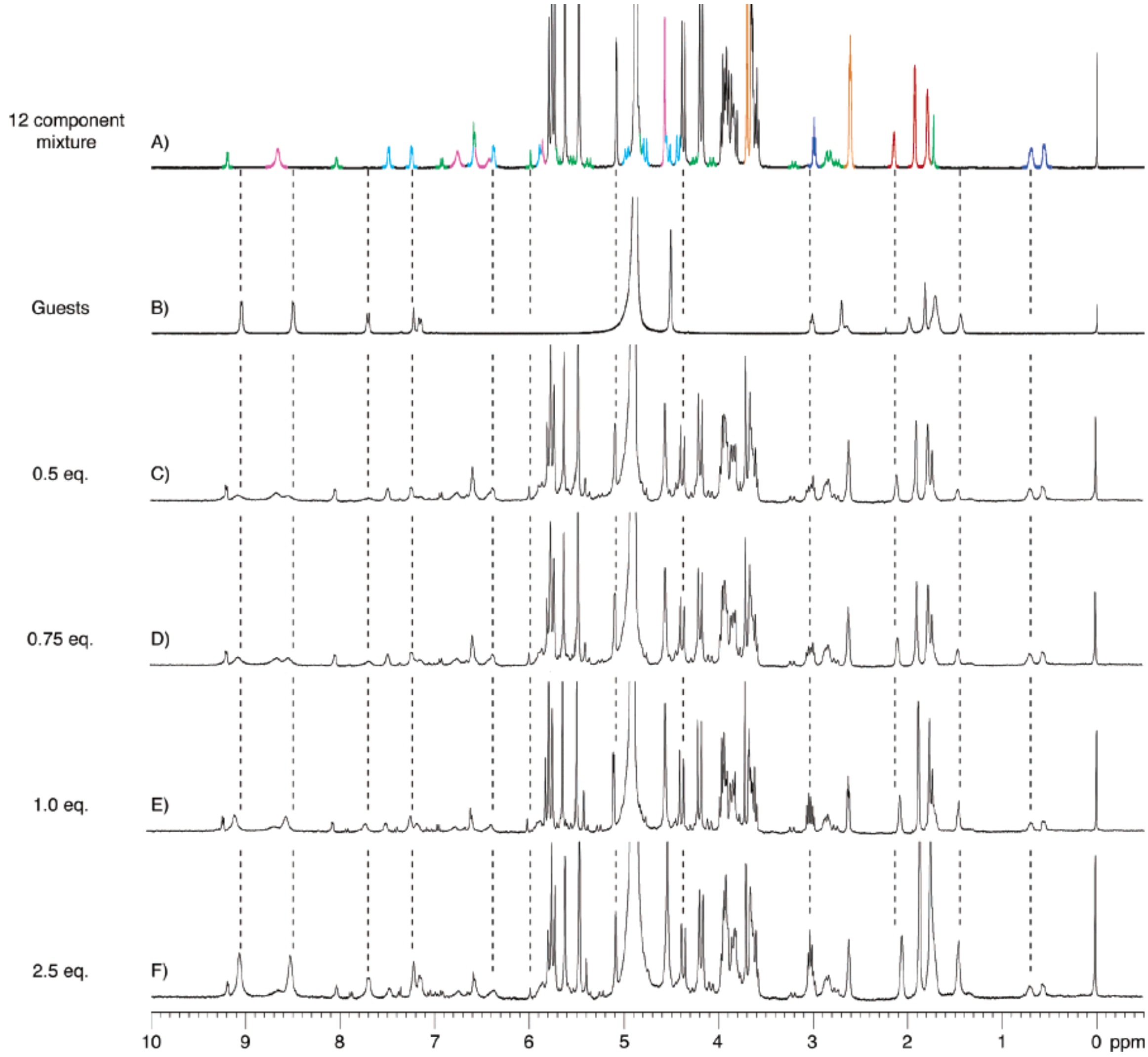


FIGURE 5. ^{1}H NMR spectra (500 MHz, D_2O, pD 7.4) recorded for (A) a self-sorted mixture of **1**−**11** and KCl (1 mM); (B) an equimolar mixture of guests **3**−**5**, **10**, **11**, and KCl; (C) the self-sorted mixture of **1**−**11** and KCl upon addition of 0.5 equiv of guests **3**−**5**, **10**, **11**, and KCl; (D) upon addition of 0.75 equiv of the guests; (E) upon addition of 1.0 equiv of the guests; and (F) upon addition of 2.5 equiv of the guests. The dashed lines are intended to guide the eye along key guest resonances.

M since K_{AM} is 10^4 greater than K_{AN}, and host B selects guest M since K_{BM} is 10-fold greater than K_{BN}. When the guest concentration is greater than the host concentration, AM and BM are dominant. The consequence is that social self-sorting systems may change partners over a relatively narrow concentration range, which makes them potentially attractive in chemical sensing and artificial regulatory applications.

Experiment. How does the social self-sorting system comprising **1**−**11** and KCl respond to relative stoichiometry? Figure 5A,B shows the ^{1}H NMR spectra recorded for the 12-component self-sorted mixture and for a solution containing only the guests (**3**−**5**, **10**, **11**, and KCl). The ^{1}H NMR spectrum of the mixture of the guests shows that some remain monomeric (**4**, **5**, **11**, and KCl), whereas others socialize (**3** and **10**). Figure 5C−F shows the ^{1}H NMR spectra recorded in the presence of an excess of guests ([**3**] = [**4**] = [**5**] = [**10**] = [**11**] = [KCl] = 1.5, 1.75, 2.0, and 3.5 mM). The resonances for the majority of the complexes are unchanged ($\mathbf{1}\cdot K^+$, $\mathbf{2}_2$, **6·3**, **8·4·5**, and $\mathbf{9}_2\cdot\mathbf{10}_2$) aside from some exchange induced broadening, whereas the resonances for **7·11** are in the fast exchange regime on the chemical shift time scale and undergo changes in chemical shift with increasing concentrations of **11**. Resonances for the free guests **3**−**5** and **11** become increasingly apparent at the higher guest concentrations.[30] In addition to these readily identified resonances, new resonances become apparent at 7.9, 7.4, 7.0−7.1, 6.65, 5.4, and 5.25 ppm. While we have not been able to completely assign these resonances to specific competing aggregates, we note that several of these resonances are present in the spectrum of the two-component mixture comprising **1** and **4**. The social self-sorting system comprising **1**−**11** and KCl is more similar to the behavior simulated in Figure 3 than in Figure 4. In general, it should be easier to prepare systems that follow the behavior of Figure 3 rather than Figure 4 since fewer constraints involving equilibrium constants need to be simultaneously satisfied.

---

(30) The methyl group resonance of **5** appears at an averaged chemical shift despite the fact that well-separated resonances for the aromatic protons of its complex (**8·4·5**) and free **5** are visible because the methyl resonance does not undergo a large change in chemical shift upon complex formation.

Conclusions

Despite the wide variety of natural self-sorting systems, there are still relatively few synthetic systems that exhibit self-sorting and even fewer that do so within complex mixtures. We recently demonstrated that the preparation of an eight-component narcissistic self-sorting system in $CDCl_3$ based on H-bonding interactions is as simple as selecting the monomers from a series of well-defined aggregates from the literature. Given the strength and directionality of hydrogen bonds, it was questionable whether this approach could be transferred to self-sorting in aqueous solution where less directional electrostatic interactions and the hydrophobic effect are important driving forces. In this paper, we prepared a 12-component social self-sorting system in aqueous solution driven by a combination of metal–ligand interactions, electrostatic interactions, and the hydrophobic effect. In aqueous solution, size, shape, and stereoelectronic complementarity between components play important roles in achieving a unique set of aggregates at equilibrium. The preparation of social self-sorting systems in water is as straightforward as selecting the molecular components from a series of well-defined host–guest pairs from the literature.

Unlike narcissistic self-sorting systems that are based on the high affinity of molecules for themselves (self-association), social self-sorting systems are based on high affinity for other member(s) of the mixture. In this paper, we presented a 12-component thermodynamically controlled social self-sorting system consisting of six well-defined host–guest pairs. Similar to single host–guest complexes, the 12-component mixture is responsive to changes in temperature, pH, concentration, and host/guest stoichiometry. Unlike single host–guest complexes, however, the behavior of complex molecular ensembles will generally exceed those of their constituents due to crossover interactions between components. For example, the 12-component social self-sorting system undergoes kinetically controlled irreversible processes in response to changes in temperature—an emergent property—that was not observed for its individual components. Simulations of other social self-sorting systems show that they are capable of responding to changes in host/guest stoichiometry over narrow ranges suggesting their potential utility in chemical sensing applications.

Biological self-sorting systems respond to stimuli from their environment and exhibit adaptive and evolutionary behavior. With straightforward access to abiotic thermodynamically controlled narcissistic and social self-sorting systems in organic and aqueous solution, their use in adaptive supramolecular systems can be envisioned. The development of efficient methods—whether based on chemical, photochemical, or electrochemical stimuli—for the control of these systems under thermodynamic and kinetic conditions has the potential to result in synthetic supramolecular systems that exhibit some of the complexity of their natural counterparts.

Experimental Section

General. General experimental procedures have been described previously.[31]

Materials. Compounds **1**, **3**–**5**, **7**, **8**, and **11** are commercially available. The synthesis and characterization of **2** is described in the Supporting Information. Compounds **6**,[32] **9**,[14] and **10**[33] were prepared according to the literature procedures.

Sample Preparation. The mixtures described in this paper were prepared as follows: (1) the calculated amounts of each component were weighed out separately and transferred to a 5 mL screw cap vial, (2) D_2O (2 mL) was added, (3) the mixture was sonicated or vortexed for several minutes, (4) the pD was adjusted using concentrated KOD or DCl solution, (5) the solution was stirred at room temperature overnight, (6) the solution was centrifuged, and (7) the solution was transferred to an NMR tube for analysis. Samples for variable pD, variable concentration, and guest addition experiments were prepared similarly.

NMR Experiments. NMR spectra were measured on spectrometers operating at 400 or 500 MHz for ^1H and 100 or 125 MHz for ^{13}C. Temperature was controlled to ±0.5 K. All spectra are referenced relative to external $(CD_3)_3SiCD_2CD_2CO_2D$.

Simulations. All simulations were performed on a PC running MATLAB 6.1 (The MathWorks, Natick, MA).

Acknowledgment. We thank the National Institutes of Health (GM61854) for financial support and Dr. Anthony Day for a generous sample of **8**. L.I. is a Cottrell Scholar of Research Corporation.

Supporting Information Available: Synthetic procedures, characterization data, and ^1H and ^{13}C NMR spectra for **2**, programs used for the simulations, and ^1H NMR spectra obtained in crossover aggregation, variable temperature, variable pD, and variable concentration experiments (Figures S1–S4). This material is available free of charge via the Internet at http://pubs.acs.org.

JO049976A

---

(31) Chakraborty, A.; Wu, A.; Witt, D.; Lagona, J.; Fettinger, J. C.; Isaacs, L. *J. Am. Chem. Soc.* **2002**, *124*, 8297–8306.

(32) Buschmann, H.-J.; Fink, H.; Schollmeyer, E. Preparation of cucurbituril. German patent DE 196 03 377 A1, 1997.

(33) Fujita, M.; Yazaki, J.; Ogura, K. *J. Am. Chem. Soc.* **1990**, *112*, 5645–5647.