

Self-Sorting: The Exception or the Rule?

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Abstract: In this paper, we pose the question of whether self-sorting in designed systems is exceptional behavior or whether it is likely to become a more general phenomenon governing molecular recognition and self-assembly. To address this question we prepared a mixture comprising two of Davis' self-assembled ionophores, Rebek's tennis ball and calixarene tetraurea capsule, Meijer's ureidopyrimidinone, Reinhoudt's calixarene bis(rossette), and two molecular clips in CDCl_3 solution and observed the behavior of this ensemble by ^1H NMR. As hypothesized, high-fidelity self-sorting behavior was observed. The influence of several key variables—temperature, concentration, equilibrium constants, and the presence of competitors—on the fidelity of self-sorting is described. These results show that self-sorting is neither the exception nor the rule. They suggest, however, that the subset of known molecular aggregates that exceed the criteria required for thermodynamic self-sorting is larger than previously appreciated and potentially quite broad.

Introduction

Self-sorting—the high-fidelity recognition of self, from nonself—has been observed in a small number of designed molecular systems but is commonplace in biological systems. Self-sorting systems are capable of operating simultaneously and orthogonally within complex mixtures and, therefore, will become important programmed components in synthetic self-organizing systems.¹ To date, self-sorting systems have been based on the formation of hydrogen bonds,² metal–ligand interactions,³ solvophobic effects,⁴ and reversible covalent bonds.⁵ In these unusual systems, closely related sets of up to four different molecules^{3a} aggregate exclusively with themselves, ignoring other molecules present in the mixture. In this paper, we question whether self-sorting in designed systems is exceptional behavior or whether, just like in nature, ensembles of molecules will routinely perform their designated functions even in complex mixtures.⁶ Will mixtures of the components

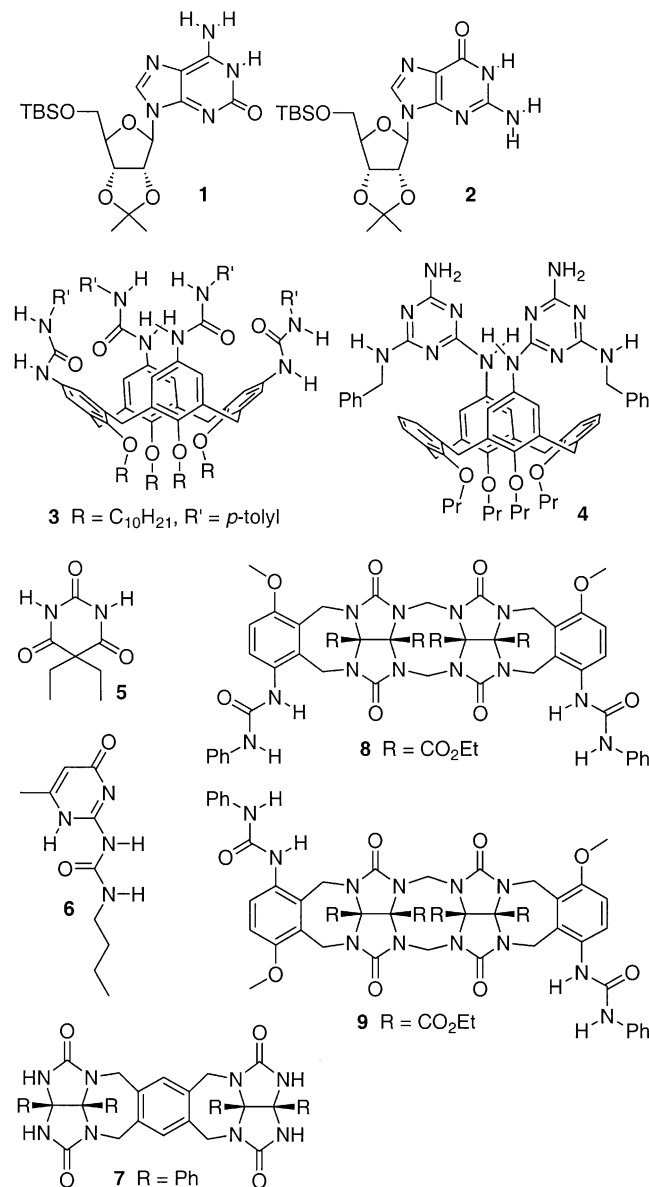
of well-known aggregates undergo self-sorting due to their distinct molecular shapes and H-bonding patterns or will crossover heteromeric aggregates be formed? Is self-sorting the exception or the rule?

Self-sorting systems can be constructed based on thermodynamic or kinetic considerations. Accordingly, we subdivide self-sorting systems into those displaying *thermodynamic self-sorting* and *kinetic self-sorting*. We define a system as being thermodynamically self-sorting if it has attained thermodynamic equilibrium and displays self-sorting. We define all other systems as being kinetically self-sorting systems. The self-sorting of sets of molecules into a small number of well-defined molecular aggregates can occur by either homomeric or heteromeric aggregation processes. In homomeric aggregation (self-association) processes, molecules display a high affinity for themselves; accordingly, this type of self-sorting process is referred to as *narcissistic self-sorting*.^{3e} We consider enantiomeric self-recognition to be a special case of narcissistic self-sorting.⁷ In heteromeric aggregation processes, molecules display a high affinity for others; we propose that this type of self-sorting be referred to as *social self-sorting*.⁸ In this paper, we only consider thermodynamic self-sorting systems.

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Results and Discussion

Eight Component Self-Sorted Mixture. Do the components of well-defined H-bonded aggregates contain sufficient information encoded within their molecular shapes and patterns of their H-bonding groups to form those aggregates even in complex mixtures containing potentially competing instructions? To address this question, we examined the behavior of **1–9** and



barium picrate by ¹H NMR.⁹ Figure 1 shows the H-bonding region (8.0–14.5 ppm) of the ¹H NMR spectra measured for **1**₁₀·Ba²⁺ + 2Pic⁻,^{2b} **2**₁₆·2Ba²⁺·4Pic⁻,^{2b} **3**₂,^{10a} **4**₃·**5**₆,^{2a} **6**₂,¹¹ **7**₂,^{10b,c} **8**₂, and **9**₂ prepared individually in CDCl₃ solution. In accord with the literature reports, each of these molecules undergoes

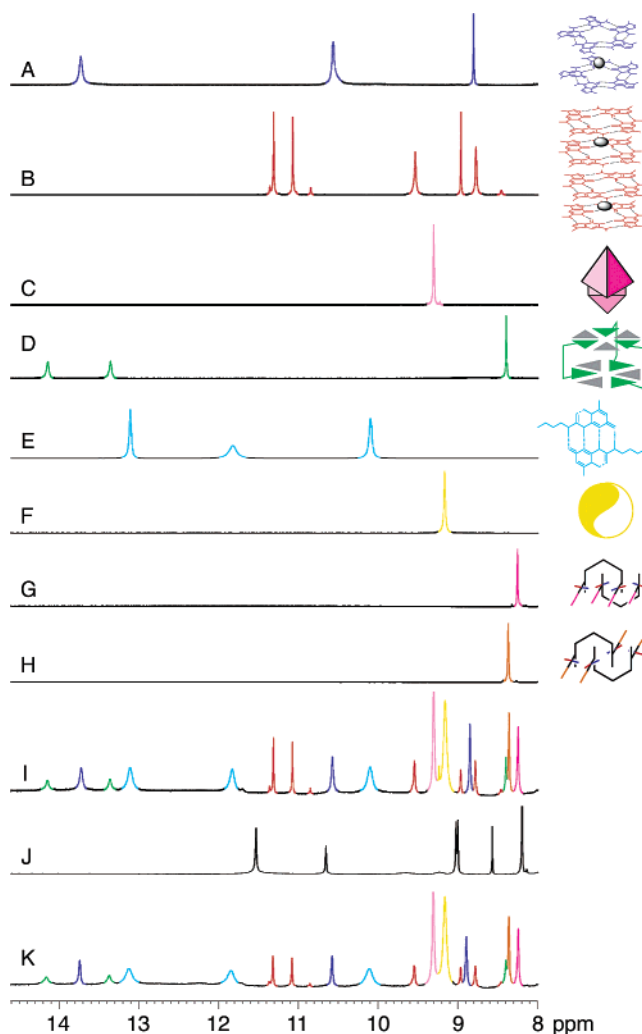


Figure 1. Hydrogen bonding region (8.0–14.5 ppm) of the ¹H NMR spectra (H₂O sat. CDCl₃, 500 MHz, [1] = [2] = [3] = [4] = [7] = [8] = [9] = 5 mM, [5] = [6] = 10 mM, 298 K) recorded for (A) **1**₁₀·Ba²⁺ + 2 Pic⁻, (B) **2**₁₆·2Ba²⁺·4Pic⁻, (C) **3**₂, (D) **4**₃·**5**₆, (E) **6**₂, (F) **7**₂, (G) **8**₂, (H) **9**₂, (I) a self-sorted mixture of **1**₁₀·Ba²⁺ + 2 Pic⁻, **2**₁₆·2Ba²⁺·4Pic⁻, **3**₂, **4**₃·**5**₆, **6**₂, **7**₂, **8**₂, and **9**₂, (J) the mixture after removal of CDCl₃ (DMSO-*d*₆, 500 MHz, 298K), (K) the mixture after removal of DMSO-*d*₆ (CDCl₃, 500 MHz, 298 K). The schematic representations depict the species present in solution and their geometries. The resonances are color coded to aid comparison.

self-assembly processes to generate well-defined aggregates. Small peaks corresponding to unidentified species were observed for **2**₁₆·2Ba²⁺·2Pic⁻, **3**₂, **8**₂, and **9**₂ (Figure 1, parts B, C, G, and H). The spectrum recorded for **7**₂ (Figure 1F) is clean, although a second resonance was often observed ~0.05 ppm downfield of the major resonance. This resonance, due to gas encapsulation^{10c} could be removed by cycles of concentration and heating at high vacuum. We next prepared a mixture of **1–9** in CDCl₃ and used this solution to extract barium picrate from water. Remarkably, the ¹H NMR spectrum of this mixture (Figure 1I) is nearly the superposition of the ¹H NMR spectra of the individual aggregates. There are, however, three changes in the spectrum that should be noted. First, a new resonance

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(9) There are several analytical techniques that could, in theory, be used to observe self-sorting based on the formation of H-bonds (¹H NMR, ¹³C NMR, IR, UV-vis, Fluorescence, GPC, or electrospray mass spectrometry). Among these alternatives, ¹H NMR is best suited to investigate complex mixtures of H-bonded aggregates because of its excellent signal dispersion, good sensitivity, and nearly universal applicability. One drawback of ¹H NMR is that it is unable to detect minor species (<3%). This limitation is probably larger in this study since crossover aggregates are likely to be less symmetrical than the self-sorted species.

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appears at ~ 9.25 ppm which we attribute to gas encapsulation in 7_2 . Second, small shoulders were detected on the resonances at 14.1, 13.4, and 11.7 ppm which could correspond to small amounts of heteromeric assemblies. Third, the chemical shift of unbound picrate shifts from 8.81 to 8.86 ppm (Figure 1, parts A and I). The spectrum of a mixture of $1_{10} \cdot \text{Ba}^{2+} + 2\text{Pic}^-$ and $2_{16} \cdot 2\text{Ba}^{2+} \cdot 4\text{Pic}^-$ also shows changes in the chemical shift of unbound picrate. These results demonstrate that by simply selecting monomers from classic examples of self-assembling species it is possible to generate complex mixtures that exhibit a high degree of self-sorting.

Despite the fact that several of these aggregates are known to undergo fast chemical exchange of their subunits on the laboratory time scale, we wanted to obtain direct evidence that the observed self-sorting was due to thermodynamic rather than kinetic preferences. For this purpose, we concentrated the self-sorted mixture to dryness and redissolved the mixture in $\text{DMSO-}d_6$ (Figure 1J) which competes efficiently for H-bond donors and disrupts the aggregates. After concentration the mixture was then redissolved in CDCl_3 . The ^1H NMR spectrum shown in Figure 1K is indistinguishable from that shown in Figure 1I. This control experiment allows us to exclude the possibility of kinetic self-sorting and conclude that thermodynamic self-sorting operates in this system.

In selecting **1–9** we were limited to compounds that could be easily prepared, that could be obtained from other investigators, or that were already available in our laboratory. Because we used ^1H NMR to monitor the self-sorting process, we were also limited to selecting aggregates whose diagnostic H-bonded resonances did not overlap. Despite these limitations, we believe we have offered this mixture sufficient opportunity for crossover. For example, **7** could H-bond to the glycoluril O-atoms of molecular clips **8** and **9**. Similarly, calixarenes **3** and **4** could have formed heterodimers. The mixture of **1–9** and barium picrate is unlikely to represent a special case.

Variables that Affect the Fidelity of Self-Sorting Processes.

Many variables can alter the outcome of self-sorting experiments (solvent, temperature, equilibrium constants, concentration, number of components, competitors, etc). We explore several of these variables by simulation and experiment.

Temperature. Self-assembly processes are sensitive to changes in temperature since the equilibrium constants governing their formation and rates of dynamic exchange processes are temperature dependent. In variable temperature ^1H NMR measurements small changes in temperature can lead to large spectral changes which often allow the observation of minor components, whether those be distinct species or conformational isomers.¹² Figure 2 shows the ^1H NMR spectra measured for the 8-component mixture between 263 and 323 K. As the temperature is raised from 298 to 323 K the resonances for **4**₃, **5**₆ and **6**₂ broaden dramatically. In contrast, the H-bonded resonances for **3**₂, **7**₂, **8**₂, and **9**₂ remain sharp indicating the high stability of these dimers. As the temperature is lowered from 298 to 263 K (Figure 2A), the majority of the resonances sharpen probably due to a reduction in the rate of dynamic exchange processes. The observation of significant new resonances at low temperature would be indicative of crossover aggregates whose resonances become time averaged with the resonances for the self-sorted species at room temperature. The

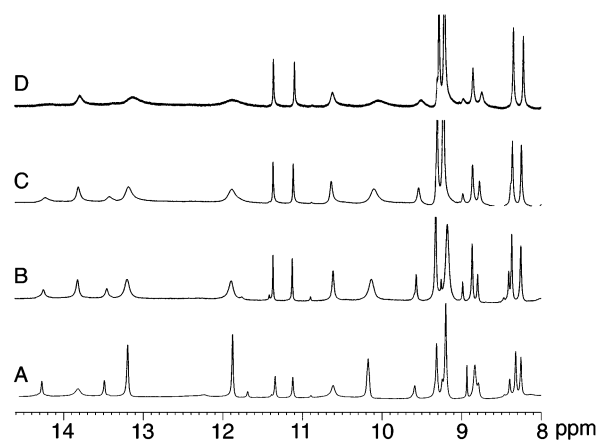


Figure 2. Hydrogen bonding region (8.0–14.5 ppm) of the ^1H NMR spectra (H_2O sat. CDCl_3 , 500 MHz) recorded for the self-sorted mixture of $1_{10} \cdot \text{Ba}^{2+} + 2\text{Pic}^-$, $2_{16} \cdot 2\text{Ba}^{2+} \cdot 4\text{Pic}^-$, **3**₂, **4**₃, **5**₆, **6**₂, **7**₂, **8**₂, and **9**₂ at (A) 263 K, (B) 298 K, (C) 308 K, and (D) 323 K.

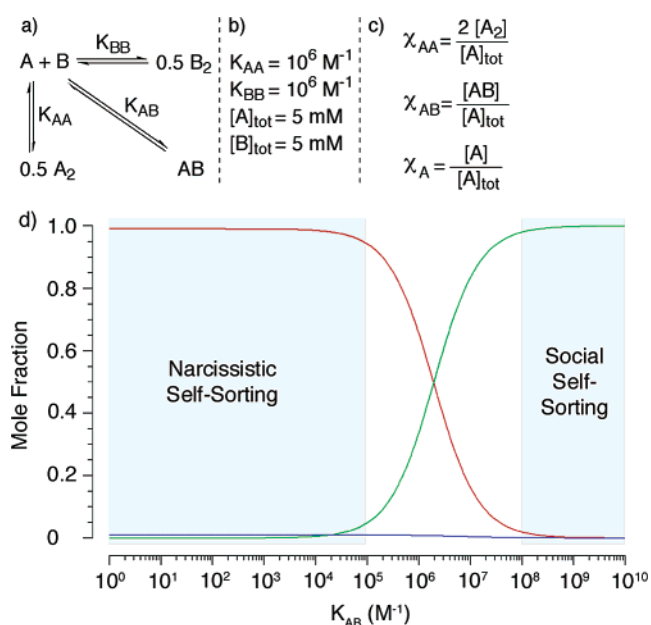


Figure 3. Degree of self-sorting in a two component mixture depends on K_{AB} : (a) equilibria considered, (b) constraints imposed, (c) mole fraction definitions, and (d) a plot of mole fraction versus K_{AB} . Legend: χ_{AA} , red; χ_{AB} , green; χ_A , blue.

small, broad resonances at 11.7 and 12.2 ppm and the rolling baseline near the resonances at ~ 14.2 and 13.5 most likely represent crossover aggregates. Although this experiment does not allow us to provide a quantitative measure of the degree of self-sorting, it does allow us to conclude that self-sorting predominates in this system.¹³

Equilibrium Constants. How large a difference between the equilibrium constants for homomeric versus heteromeric aggregation is sufficient to drive self-sorting? To address this question, we performed simulations of the simple two component system described in Figure 3a comprising monomers (A and B), homodimers (A_2 and B_2), and a heterodimer (AB) whose

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(13) We attempted to observe crossover aggregates by subtracting the ^1H NMR spectra of the individual components from that of the mixture. Unfortunately, spectral broadening in the mixture which can be due to either dynamic exchange processes within the homomeric aggregates or crossover heteromeric aggregates, makes spectral subtraction uninformative. We also performed EXSY and selective 1D ROESY experiments, but did not observe signals that could be assigned to crossover aggregates.

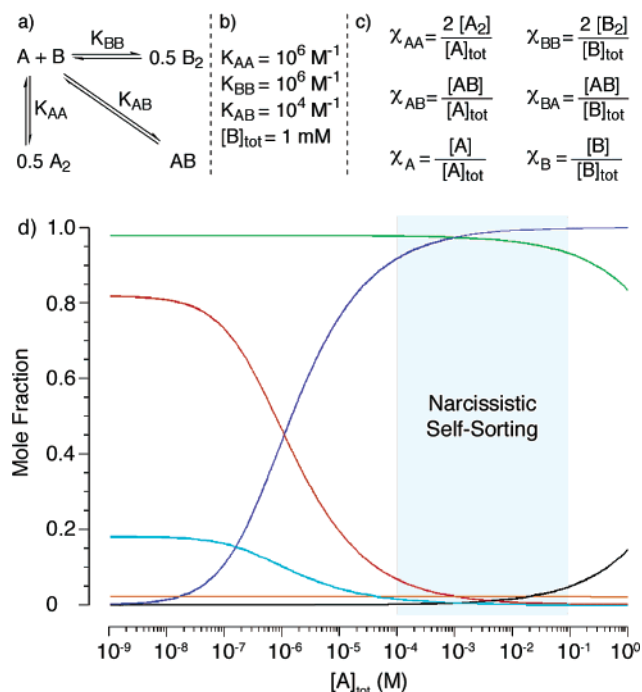


Figure 4. Degree of self-sorting in a two component mixture depends on $[A]_{\text{tot}}$: (a) equilibria considered, (b) constraints imposed, (c) mole fraction definitions, and (d) a plot of mole fraction versus $[A]_{\text{tot}}$. Legend: χ_{AA} , blue; χ_{BB} , green; χ_{AB} , aqua; χ_{BA} , black; χ_A , red; χ_B , orange.

equilibria are governed by three equilibrium constants (K_{AA} , K_{BB} , and K_{AB}). We impose constraints on the total concentrations of A and B ($[A]_{\text{tot}}$ and $[B]_{\text{tot}}$) and fix the values of K_{AA} (10^6 M^{-1}) and K_{BB} (10^6 M^{-1}) as outlined in Figure 3b. Figure 3d shows a plot of mole fraction versus K_{AB} .¹⁴ At low values of K_{AB} ($0 < K_{AB} < 10^4 \text{ M}^{-1}$), self-sorting is highly efficient and the homodimers represent greater than 98% of the mixture. A 100-fold difference in equilibrium constant is more than sufficient to drive narcissistic self-sorting. When K_{AB} is 10-fold lower than K_{AA} , $\chi_{AA} \approx 0.94$; narcissistic self-sorting is efficient with only a 10-fold difference in equilibrium constant! As the values of K_{AA} and K_{BB} increase (decrease), the curves for χ_{AA} and χ_{AB} shift to the right (left) but the 10-fold difference in equilibrium constant needed to drive self-sorting remains unchanged (curves not shown). When K_{AB} exceeds 10^8 M^{-1} the heterodimer AB is formed preferentially and social self-sorting dominates.

Concentration. Concentration has a dramatic effect on the extent of chemical interactions at thermodynamic equilibrium. Because ^1H NMR is not particularly useful when investigating minor components of a mixture, we performed simulations. Consider the system outlined in Figure 4a subject to the constraints given in Figure 4b. The value of $[B]_{\text{tot}}$ was chosen such that it was 1000-fold greater than K_{BB}^{-1} to ensure dimerization in the absence of A. Figure 4d shows a plot of mole fraction of the components versus $[A]_{\text{tot}}$. When $[A]_{\text{tot}} < 10^{-7} \text{ M}$ approximately 80% of A is monomeric and 20% is heterodimeric (AB). For small values of $[A]_{\text{tot}}$, self-association of A is less favorable than association with B even though K_{AB} is 100-fold lower than K_{AA} . As the value of $[A]_{\text{tot}}$ approaches K_{AA}^{-1} , homodimerization competes with heterodimerization, χ_A and χ_{AB} decrease, and χ_{AA} increases. When $[A]_{\text{tot}}$ is comparable

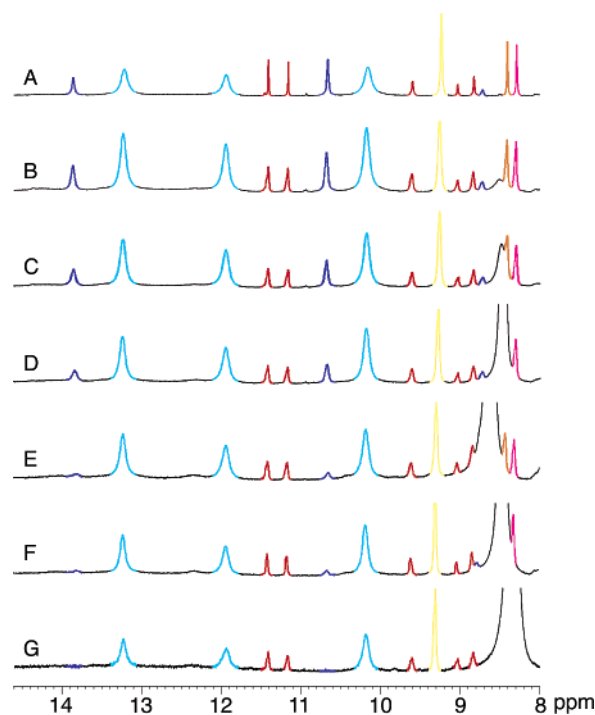


Figure 5. Hydrogen bonding region (8.0–14.5 ppm) of the ^1H NMR spectra recorded for a six component mixture comprising $1_{10}\cdot\text{Ba}^{2+} + 2 \text{ Pic}^-$, $2_{16}\cdot 2\text{Ba}^{2+}\cdot 4\text{Pic}^-$, 6_2 , 7_2 , 8_2 , and 9_2 (H_2O sat. CDCl_3 , 500 MHz, 5 mM, 298 K) in the presence of increasing concentrations of **5**: (A) **5** = 0 mM, (B) **5** = 1 mM, (C) **5** = 2 mM, (D) **5** = 5 mM, (E) **5** = 10 mM, (F) **5** = 20 mM, and (G) **5** = 40 mM. The resonances are color coded as in Figure 1 to aid comparison.

to $[B]_{\text{tot}}$ ($10^{-4} \text{ M} < [A]_{\text{tot}} < 10^{-1} \text{ M}$), both χ_{AA} and χ_{BB} exceed 0.9 and narcissistic self-sorting dominates. When $[A]_{\text{tot}}$ far exceeds $[B]_{\text{tot}}$ ($A_{\text{tot}} > 1 \text{ M}$), the homodimerization of B cannot compete with heterodimerization and χ_{BB} falls as χ_{BA} increases.

The value of $[A]_{\text{tot}}$ at which the χ_{AA} and χ_{BB} curves intersect is the point at which self-sorting is mutually efficient. This crossing always occurs when $[A]_{\text{tot}} = [B]_{\text{tot}}$. Even though this conclusion is perhaps not surprising to those fully acquainted with thermodynamics, it represents a useful rule-of-thumb for scientists interested in constructing complex self-sorting systems: self-sorting is most efficient when all components are present at the same concentration.

The 1000-fold range (10^{-4} – 10^{-1} M) over which narcissistic self-sorting dominates should be sufficient for many applications. In other applications, for example as components of adaptive mixtures,¹ it would be useful to control the concentration range over which self-sorting is efficient. We find that the relative value of K_{AB} controls this concentration range. For example, as the value of K_{AB} is increased to 10^5 M^{-1} , the region in which narcissistic self-sorting is efficient becomes more narrow ($0.0005 \text{ M} < [A]_{\text{tot}} < 0.002$). Conversely, when K_{AB} is decreased (10^3 M^{-1}) narcissistic self-sorting is efficient over a broader range of concentration ($0.00005 \text{ M} < A_{\text{tot}} < 1 \text{ M}$).

Competitive Hydrogen Bonding Species. A common rule-of-thumb in the design of self-assembled aggregates is that no hydrogen bond donors should be left unsatisfied. Similarly, the presence of unpaired species in a self-sorting experiment might wreak havoc. We tested the ability of a self-sorted mixture comprising $1_{10}\cdot\text{Ba}^{2+} + 2 \text{ Pic}^-$, $2_{16}\cdot 2\text{Ba}^{2+}\cdot 4\text{Pic}^-$, 6_2 , 7_2 , 8_2 , and 9_2 to resist the presence of **5** as competitor (Figure 5). In the absence of **5** (Figure 5A) self-sorting is observed. As the concentration of **5** is increased to 40 mM (Figure 5, parts B–G),

(14) We do not plot χ_{BB} , χ_{BA} , and χ_B because they are identical to χ_{AA} , χ_{AB} , and χ_A under the constraints employed.

however, clear changes in the spectrum occur. Aggregate $1_{10} \cdot \text{Ba}^{2+} + 2 \text{Pic}^{-}$ is not stable in the presence of **5** and its H-bonded resonances (10.7 and 13.8 ppm) decrease in intensity and then disappear. We do not observe H-bonded resonances corresponding to well-defined aggregates involving **1**; they are either obscured by the resonance for **5** between 8 and 9 ppm or are part of the rolling baseline that becomes increasingly apparent. In sharp contrast to the behavior of $1_{10} \cdot \text{Ba}^{2+} + 2 \text{Pic}^{-}$, the resonances for aggregates $2_{16} \cdot 2\text{Ba}^{2+} \cdot 4\text{Pic}^{-}$, **6**, **7**, **8**, and **9** do not change appreciably as the concentration of **5** is increased to 40 mM. Although this result shows that self-sorting can be compromised by the presence of H-bonding competitors, it also shows that some aggregates can resist their presence.

Origins of Self-Sorting in Complex Mixtures. The degree of self-sorting in complex mixtures depends on the values of each of the variables described in the previous section. If we consider the prototypical situation, in which all components are present at equal concentration well above K_d , then the relative values of the association constants play the critical role. What influences the relative values of the equilibrium constants for homomeric versus heteromeric aggregation processes? For molecular aggregation in CDCl_3 driven by the formation of hydrogen bonds, the precise pattern of hydrogen bond donors and acceptors, their spatial arrangement, and the presence of a closed network of hydrogen bonds are probably particularly important factors that favor homomeric over heteromeric aggregation processes. In aqueous solution, complementarity (shape and electrostatic) between the molecular surfaces of the components will play similarly important roles.

Conclusion

We have demonstrated that mixtures of **1–9** and barium picrate undergo thermodynamic self-sorting in CDCl_3 solution. The observed self-sorting is based on the thermodynamic preferences of the molecular ensemble rather than kinetically controlled aggregation phenomena. We explored several of the factors that influence the fidelity of the self-sorting process (temperature, equilibrium constants, concentration, and competitors) by a combination of experiment and simulation. We find that relatively small differences in equilibrium constants (>10 -fold) are sufficient to drive narcissistic self-sorting. Such narcissistic self-sorting processes are most efficient when the concentrations of all the components are equal. Although the results of these simulations suggest conditions where self-sorting will be efficient, they also suggest conditions where self-sorting will be inefficient. For example, when: (1) the concentration of one of the components far exceeds the concentrations of the other components, (2) the difference between the association constants for homomeric and heteromeric is small (<10 -fold), or (3) competitive hydrogen bonding species are present, the fidelity of the self-sorting process may be compromised. In addition, self-sorting mixtures will continue to be subject to the limitations of the individual assemblies. We do not, therefore, expect to observe self-sorting under conditions (solvent, temperature, etc.) where the individual aggregates are not stable. The continued development of supramolecular chemistry, however, will undoubtedly produce aggregates that display high stability under many sets of conditions that will ease these limitations.

Even though the present demonstration comprised only 10 molecular components generating eight molecular aggregates held together by hydrogen bonds and ion–dipole interactions

in CDCl_3 solution the implications are potentially broad. For example, the preparation of self-sorting mixtures comprising significantly larger numbers of compounds should be possible provided that each selected component has a unique pattern or arrangement of its H-bonding groups. An examination of natural systems suggests that self-sorting will not be confined to organic solvents or to assemblies driven by hydrogen bonds. Rather, we expect that self-sorting will also become commonplace for molecular aggregation in aqueous and polar organic solutions driven by the hydrophobic effect, metal–ligand interactions, and electrostatic interactions.

The title question remains. Is self-sorting the exception or the rule? The results presented here show that self-sorting is neither the exception nor the rule. The results do suggest, however, that the subset of known molecular aggregates that exceed the criteria required for thermodynamic self-sorting is larger than previously appreciated and potentially quite broad. This realization, in turn, offers a straightforward method for the preparation of complex, potentially functional, self-sorting systems.

Experimental Section

Materials. Compounds **1**, **2**, barium picrate, **3**, and **4** were prepared in the laboratories of Professors Jeffery Davis, Julius Rebek, Jr., and David Reinhoudt. Compound **5** was commercially available whereas **6** and **7** were prepared according to literature procedures. The synthesis and characterization of **8** and **9** are described in detail in the Supporting Information.

Sample Preparation. Aggregates **3**, **4**, **5**, **6**, **7**, **8**, and **9** were prepared by weighing the calculated amounts of their components into 5 mL screw cap vials followed by the addition of CDCl_3 (1 mL). Water (1 mL) was added and the biphasic mixture was stirred at RT for 24 h, the CDCl_3 layer pipetted off, centrifuged to remove bulk water, and then transferred to an NMR tube for analysis. For the preparation of $1_{10} \cdot \text{Ba}^{2+} + 2 \text{Pic}^{-}$ and $2_{16} \cdot 2\text{Ba}^{2+} \cdot 4\text{Pic}^{-}$ the calculated quantities of **1** or **2** were dissolved in CDCl_3 (1 mL) followed by the addition of a solution of barium picrate (1.5 mg) in H_2O (1 mL). The biphasic mixture was stirred for 24 h at RT, the H_2O layer pipetted off, stirred again with a fresh portion of H_2O (1 mL), the CDCl_3 layer pipetted off, centrifuged to remove bulk water, and then transferred to an NMR tube for analysis. The 8-component mixture for the self-sorting experiments was prepared in an identical manner.

NMR Experiments. NMR spectra were measured on Bruker AM-400, DRX-400, and DMX-500 instruments operating at 400 or 500 MHz for ^1H and 100 or 125 MHz for ^{13}C . Temperature was controlled to ± 0.5 K with a Bruker eurotherm module. All spectra are referenced relative to residual CHCl_3 .

Simulations. All simulations were performed on a PC running Scientist (MicroMath Scientific Software, Salt Lake City, Utah) under Windows 2000 Professional.

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Supporting Information Available: Synthetic procedures and characterization data for **8** and **9**, models used in the simulations, and spectra obtained in ^1H NMR subtraction and dilution experiments. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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