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Molecular Marriage through Partner Preferences in Covalent Cage Formation and Cage-to-Cage Transformation

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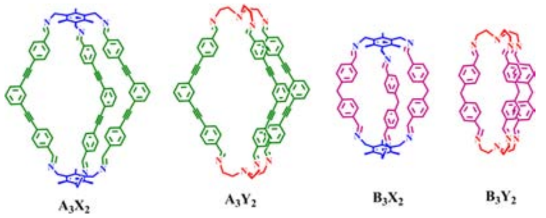
S *Supporting Information*

ABSTRACT: Unprecedented self-sorting of three-dimensional purely organic cages driven by dynamic covalent bonds is described. Four different cages were first synthesized by condensation of two triamines and two dialdehydes separately. When a mixture of all the components was allowed to react, only two cages were formed, which suggests a high-fidelity self-recognition. The issue of the preference of one triamine for a particular dialdehyde was further probed by transforming a non-preferred combination to either of the two preferred combinations by reacting it with the appropriate triamine or dialdehyde.

Nature, especially in biological systems, utilizes self-sorting to achieve *"order out of chaos"* by discriminating "self" from "non-self" in a complex reaction mixture. Self-sorting has the ability to reduce the number of components by arranging into specific high-fidelity combinations.[1] In abiological systems, non-covalent self-sorting, especially hydrogen-bonding and donor–acceptor interaction driven self-recognitions, has been widely explored.[2] Lehn, Stang, and others have reported examples of self-recognition based on dynamic coordination-driven self-assembly.[3,4] Very recently, a few examples have come up in which dynamic covalent bonds have been utilized along with metal–ligand coordination to construct self-sorted hybrid macrocycles and cages.[5] In contrast, though there are quite a few reports in the literature of self-sorted organic macrocycles, purely organic self-sorted 3D architectures have not been studied.

Purely organic three-dimensional cages can be synthesized utilizing dynamic covalent bond (such as imine bond) formation to avoid tedious multistep reactions. These porous cages have attracted much attention recently, and many of them have been utilized for various functions, such as sensing, gas storage and separation, catalysis, and drug delivery.[6,7] The dynamic bonds may potentially allow self-sorting in multicomponent systems, generating specific cages of intended multiple functionalities. This would also allow cage-to-cage transformations in solution—a very useful feature that can be utilized to change the cage system (*in situ*) when necessary. Here, we report one such attempt with two dialdehydes [**A** = 1,3-bis(4-formylphenylethynyl)benzene, **B** = bis(4-formylphenyl)methane] and two triamines [**X** = 1,3,5-tris-(aminomethyl)-2,4,6-trimethylbenzene, **Y** = tris(2-aminoethyl)-amine], which were found to form four cages (Chart 1) when treated separately in pairs but showed remarkable partner selectivity (one specific combination) when a mixture of the two triamines and one dialdehyde was used. Moreover, in a more complex situation, when all four components were allowed to react, they produced only two of the cages that were formed in the previous experiment. In other words, they combined with their preferred partners. To further establish these partner preferences, we show that a non-self-sorted cage could be transformed to either one of the self-sorted cages by allowing it to react with the appropriate triamine or dialdehyde. These transformations become viable because the bonds that assemble the components together (namely, the imine bonds) are dynamic in nature. Thus, the preferred combination of components can form in solution, even though we started from a non-preferred combination.

Chart 1



Nanoscopic organic cages $\mathbf{A_3X_2}$, $\mathbf{A_3Y_2}$, $\mathbf{B_3X_2}$, and $\mathbf{B_3Y_2}$[8] were synthesized (Supporting Information) by condensing 2 equiv of flexible triamine (**X** or **Y**) with 3 equiv of dialdehyde (**A** or **B**) in $CHCl_3$–EtOH (1:10). Products were fully characterized by ^1H NMR, ^{13}C NMR, COSY, HMQC, FTIR, and ESI-MS. These results confirmed the formation of 3:2 (dialdehyde:triamine) self-assembled cages through imine bond formation in all cases.

We were also able to crystallize the cage $\mathbf{B_3X_2}$ from its chloroform solution by *n*-pentane vapor diffusion as 2-$(\mathbf{B_3X_2})\cdot 7.5CHCl_3$. As expected, the crystal structure confirmed the 3:2 self-assembled structure of this cage. Interestingly, the asymmetric unit contains two cage molecules along with several $CHCl_3$ molecules situated both inside and outside the cage molecules. The cage is roughly ellipsoidal in shape. The distance between the centroids of the benzene rings of the triamine parts is ∼14 Å, which can be defined as the length of the cage (Figures 1a and S24).

The three methylene carbon atoms at the central part of the cage form roughly equilateral triangles of length ∼12 Å. As expected, all the imine bonds are *trans* in nature. However, the

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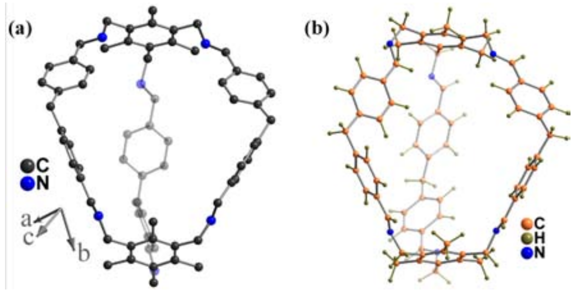


Figure 1. (a) Ball-and-stick diagram of the single-crystal X-ray structure of $\mathbf{B_3X_2}$. Hydrogen atoms and solvent molecules ($CHCl_3$) have been removed for clarity. (b) Energy-optimized [DFT, B3LYP] structure of $\mathbf{B_3X_2}$.

cages lack C_3 symmetry, as the three arms are not equivalently disposed in space. The energy-optimized (DFT, B3LYP, 631-G) structures of all four cages show them to be ellipsoidal in shape (lacking C_3 symmetry), with all the imine bonds in *trans* disposition (Figure S27), much like the crystal structure of $\mathbf{B_3X_2}$. In fact, the molecular dimensions of the cage $\mathbf{B_3X_2}$ in its crystal structure and energy-optimized geometry are remarkably similar (Figures 1b, S24, and 25). This also encouraged us to use these optimized structures and their energies as a guide to calculate theoretically the heats of the reactions as described later.

After the four cages were synthesized, the first question that came to our minds was, what would happen if two triamines (**X** and **Y**) and one dialdehyde (**A** or **B**) were present in the same reaction mixture? To address this, two sets of experiments were carried out with two triamines and one aldehyde. In a typical experiment we treated 3 equiv of **B** with a mixture of 2 equiv of **X** and 2 equiv of **Y** in $CHCl_3$–EtOH (1:10) at room temperature with stirring for 48 h. The precipitate that formed during the course of the reaction was washed with ethanol and characterized by NMR. Surprisingly, ^{1}H NMR showed exclusive formation of cage $\mathbf{B_3X_2}$ (Scheme 1). Thus, aldehyde **B** was found to select **X** as its preferred partner, although **Y** was also present in the solution in an equivalent amount. In contrast, aldehyde **A** under similar conditions displayed a remarkable preference for triamine **Y** over triamine **X** and led to the exclusive formation of cage $\mathbf{A_3Y_2}$ (Scheme 1).

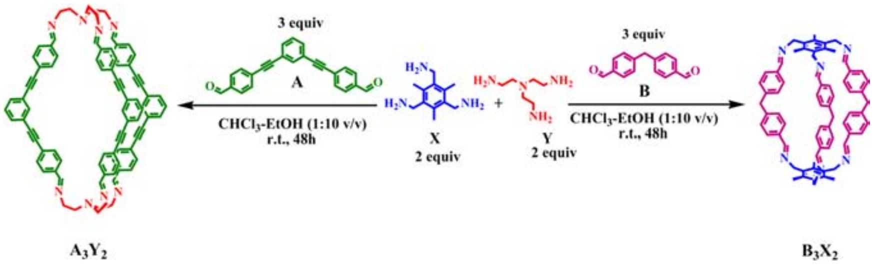
Naturally, the next question that arise from these findings is, would similar selectivity still be observed in a more complex mixture of all four components (**X**, **Y**, **A**, and **B**)? If so, then the system can be defined as a self-sorting system of four components. This kind of self-sorting of purely organic cages has so far not been explored in the literature. To address this new question, we allowed a solution of triamines **X** and **Y** to react with a mixture of dialdehydes **A** and **B** (ratio 2:2:3:3) in $CHCl_3$–EtOH (1:10 v/v) at room temperature for 24 h (Scheme 2). Despite the innumerable possibilities, ^{1}H NMR and ESI-MS (Figures 2 and S18) analyses of the precipitated mixture revealed the exclusive formation of cages $\mathbf{A_3Y_2}$ and $\mathbf{B_3X_2}$. ^{1}H NMR monitoring of the reaction shows that characteristic peaks corresponding to aldehydes **A** and **B** completely vanished, and peaks corresponding to cages $\mathbf{A_3Y_2}$ and $\mathbf{B_3X_2}$ arose during the reaction. In the initial stage of the transformation, there were several intermediate byproducts, as indicated by ^{1}H NMR. Those intermediates were gradually consumed, leading to the formation of two specific combinations among the myriad possibilities; in other words, self-sorting is observed.

All four cages are sparingly soluble in the solvent mixture [$CHCl_3$–EtOH (1:10)] used for the self-sorting experiment, so the self-sorting may be a result of the faster precipitation of two of the cages ($\mathbf{A_3Y_2}$ and $\mathbf{B_3X_2}$) as compared to the other two ($\mathbf{A_3X_2}$ and $\mathbf{B_3Y_2}$). In other words, the self-sorting may be precipitation induced.[9]

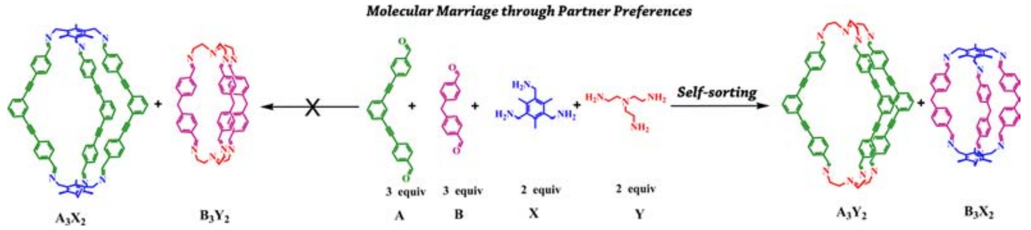
To investigate this possibility, the reaction rates of individual cage formations need to be probed, but complexities due to precipitation make any such rate constant determination unreliable for this solvent system [$CHCl_3$–EtOH (1:10)]. However, the cages are soluble in chloroform. Still, the exact rate laws could not be established due to the complexity (several uncharacterized intermediates) of the reactions. So to get a glimpse of the reaction kinetics, the individual cage formations were monitored in $CDCl_3$ for a fixed period of time. It was found that within 5 h the conversion of the individual pairs of reactants to the cages $\mathbf{A_3X_2}$, $\mathbf{A_3Y_2}$, $\mathbf{B_3X_2}$, and $\mathbf{B_3Y_2}$ was respectively 19%, 97%, 17%, and 78%. These experimental results suggested that cages $\mathbf{A_3Y_2}$ and $\mathbf{B_3Y_2}$ exhibit faster self-assembly kinetics. However, when the four-component self-sorting experiment was carried out in $CDCl_3$ (monitored by ^{1}H NMR up to 130 h, Figure S21), again only $\mathbf{A_3Y_2}$ and $\mathbf{B_3X_2}$ could be detected. So, the same two cages are self-sorted in both solvent systems. This result demonstrates that precipitation, if any, has little effect. It is also evident that the reaction rates alone cannot explain the outcome of self-sorting in chloroform. So, we performed theoretical calculations to get some insight into the energetics of these reaction processes.

Solvent effects and entropy play major roles in these reactions. However, it is very difficult to calculate theoretically the energetics of these reactions taking these factors in account. A compromise can be achieved by calculating the energy differences between the reactants (2 mol of triamine + 3 mol of dialdehyde) and the products (1 mol of the cage + 6 mol of water). This process can provide rough estimates of the heats of the reactions (ΔH_r). The optimized energies of the components involved were obtained through DFT (B3LYP,

Scheme 1



Scheme 2



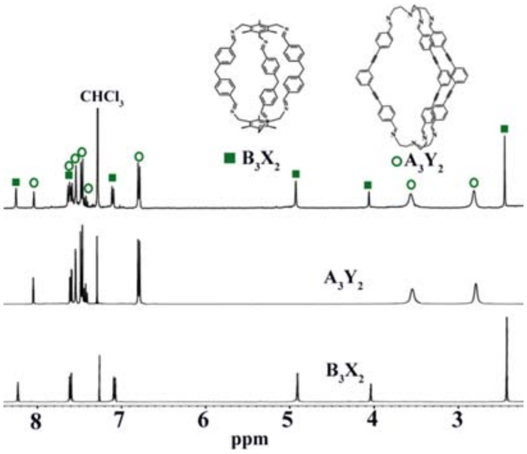


Figure 2. ^1H NMR of the precipitated mixture of products of the self-sorting experiment and the individual cages recorded in $CDCl_3$.

631-G) calculations.[10] All calculated heats of reactions were found to be positive, illustrating the crucial role played by the positive entropy changes in the cage formations. The heats of reactions range from 40 to 50 kcal/mol. According to these calculations, the formation of A_3Y_2 is slightly more energy demading than that of A_3X_2 (~2.3 kcal/mol). The calculations also revealed that the formation of B_3Y_2 is much more energy demanding (~5.9 kcal/mol) than that of B_3X_2. Therefore, A_3Y_2 and B_3Y_2 are energetically unfavored (but they form faster in solution). The self-sorting process can be thought to be two parallel reactions, with the reactants for each reaction selected by nature as preferred partners. If the overall process were kinetically controlled, a mixture of products dominated by A_3Y_2 and B_3Y_2 (as their rates of formation are considerably higher) would be expected. So, the self-sorting must be thermodynamically controlled, which can explain the formation of B_3X_2. The formation of A_3Y_2 is probably forced by the resulting unavailability of **B** and **X**. In addition, A_3Y_2 is only very slightly more energy demanding than A_3X_2 (shortcomings of the theoretical calculations regarding solvent and entropy effects must also be kept in mind). It is evident from the theoretical calculations that, in a mixture of **B**, **X**, and **Y**, the thermodynamically preferred product is B_3X_2. The addition of **A** to this mixture helps the equilibrium by removing **Y** from the solution (very fast), resulting in the overall thermodynamic preference for B_3X_2 and A_3Y_2. These results point to the well-known fact that, in self-sorting, collective behavior may not always reflect the conclusions drawn from studies on individual components or reaction system in isolation.[1]

The dynamic nature of the reaction system as well as the high-fidelity self-sorting should effect a cage-to-cage transformation. A non-self-sorted cage system (a non-preferred marriage of a triamine and a dialdehyde) is expected to convert to a self-sorted cage (preferred marriage) by exchanging either component in solution.

Cage B_3Y_2 (1 equiv) was allowed to react with dialdehyde **A** (3.5 equiv) in $CDCl_3$, which led to complete conversion to cage A_3Y_2 (Scheme 3) within 30 h at room temperature with the release of **B** (Scheme 3). ^1H NMR monitoring (Figure 3) revealed that, during the course of the transformation, characteristic aromatic peaks corresponding to cage B_3Y_2, at $\delta = 7.03$ and 7.18 ppm, completely vanished with the arrival of new characteristic peaks assigned to aromatic protons of cage A_3Y_2, at $\delta = 6.76$ and 8.01 ppm. Furthermore, ESI-MS analysis of the final reaction mixture also confirmed the formation of cage A_3Y_2 along with the presence of aldehyde **B** (Figure S22).

Scheme 3

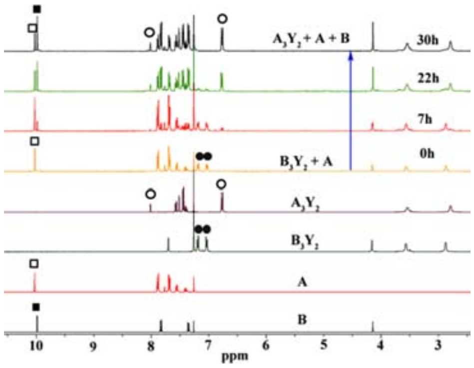


Figure 3. ^1H NMR spectra recorded over time during the transformation of cage B_3Y_2 to cage A_3Y_2 in $CDCl_3$, with spectra of the pure components involved for comparison. Peaks indicated by different symbols were used for monitoring the reaction progress.

In a similar manner, when the cage B_3Y_2 was treated with amine **X**, cage conversion took place within 115 h (Scheme 3). Formation of cage B_3X_2 was similarly confirmed by ^1H NMR (Figure S20) and ESI-MS (Figure S23) analyses. In a similar way, conversion of A_3X_2 to A_3Y_2 was very facile, though the reverse was not feasible. To the best of our knowledge, this represents the first example of cage-to-cage transformation involving purely organic imine-based assemblies.

To summarize, we were able to show, for the first time, the self-sorting behavior of a mixture of two different triamines and two different dialdehydes, to produce two specific purely organic cages out of several possibilities. The choice of partners and the involvement of the dynamic covalent bonds (imine) were established through the cage-to-cage transformations, by converting a non-self-sorted cage to two self-sorted cages by allowing it to react with its conjugate triamine and dialdehyde. Both experimental and theoretical studies were used to show and emphasize the fact that the composite behavior of these dynamical systems could hardly be rationalized on the basis of the results of an individual component's behavior in the absence of a competitor. Studies of *in situ* manipulations of the nano cages for storage, recognition, and other uses are underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Synthetic and characterization data (NMR, FTIR, ESI-MS), crystallographic details for the cage $\mathbf{B_3X_2}$, details of the DFT calculations, and single-crystal X-ray data for $\mathbf{B_3X_2}$ in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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