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Smart Macrocyclic Molecules: Induced Fit and Ultrafast Self-Sorting Inclusion Behavior through Dynamic Covalent Chemistry

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Abstract: A family of macrocycles with oligo(ethylene glycol) chains, **4O**, **5O**, and **6O**, was developed to construct a series of new incorporated macrocycles through dynamic covalent chemistry. These flexible macrocycles exhibited excellent "self-sorting" abilities with diamine compounds, which depended on the "induced-fit" rule. For instance, the host macrocycles underwent conformational modulation to accommodate the diamine guests, affording [1+1] intramolecular addition compounds regardless of the flexibility of the diamine. These macrocycles folded themselves to fit various diamines with different chain length through modulation of the flexible polyether chain, and afforded intramolecular condensation products. However, if the chain of the diamine was too long and rigid, oligomers or polymers were obtained from the mixture of the macromolecule and the diamine. All results demonstrated that inclusion compounds involving conformationally suitable aromatic diamines were thermodynamically favorable candidates in the mixture due to the restriction of the macrocycle size. Furthermore, kinetic and thermodynamic studies of self-sorting behaviors of both mixed **4O–5O** and **4O–6O** systems were investigated in detail. Finally, theoretical calculations were also employed to further understand such self-sorting behavior, and indicated that the large enthalpy change of $H_2NArArNH_2$@**4O** is the driving force for the sorting behavior. Our system may provide a model to further understand the principle of biomolecules with high specificity due only to their conformational self-adjusting ability.

Keywords: dynamic covalent chemistry · host–guest systems · macrocycles · molecular recognition · self-sorting

Introduction

Many artificial host–guest systems are designed to mimic biochemical processes in nature, which often exhibit excellent recognition and high specificity. The notion that each protein (host) recognition site has a different binding affinity to a precisely specific ligand (guest) molecule was called the "lock-and-key" principle by Fischer in 1894,[1] and is still an important requirement for rational design of drugs or host–guest systems. However, according to the "induced-fit" hypothesis,[2] the hosts and guests need not exhibit precisely complementary interaction, and different functions could be achieved through a single interaction.[3] In these processes, adaptation, such as dramatic conformation changes of flexible molecules upon complex formation, plays a very important role. For example, the ubiquitin molecule is important in many cellular signaling process such as protein degradation, and is recognized by a broad variety of proteins with high specificity only by means of their conformational self-adjusting ability.[4]

Considerable interest has been paid to artificial macrocyclic compounds[5] due to their intriguing topology,[6] which mimics the biological process. These compounds have potential applications in molecular recognition,[7] ion transport,[8] chemosensing and imaging,[9] and construction of molecular machines.[10] However, to go beyond the lock-and-key principle to reach high selectivity, the design of the cavity size

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and conformational flexibility of target macrocycles are greatly limited. In addition, most host–guest systems are mainly based on noncovalent interactions, but one drawback of this strategy is their low stability. Because the association constant is dependent on environment, any change in the temperature, composition, or pH of the solution may affect the equilibrium of the system.

As a result, developing a smart artificial system mimicking a biosystem by following the induced-fit principle is still a challenge. Herein we report a facile route to a series of flexible macrocycles containing two formyl groups, which can condense with amino groups to give imines in the spirit of dynamic covalent chemistry (DCC),[11] in which DCC refers to the reversible formation of chemical bonds, which tends to give the thermodynamically most stable products. Encouraged by its "error-checking" nature, many efforts have been devoted to constructing complex architectures by DCC, including macrocycles,[12] rotaxanes or catenanes,[13] and nanocages.[14] The series of macrocycles presented here can be condensed with suitable diamine compounds to give [1+1] inclusion products under both kinetic and thermodynamic control. It is not surprising that the products are thermodynamically favored ones, but the fact that they are also the kinetic ones is interesting. Moreover, owing to a length limit, a specific macrocycle exhibits different behavior in incorporation of diamines. For example, if the diamine chain is longer than the limit, flexible diamines may readjust their conformation to fit the macrocycle cavity size and give [1+1] inclusion products, while rigid ones can not. However, when the chain length of the diamine is shorter than the limit, all diamines afford inclusion products with these macrocycles.

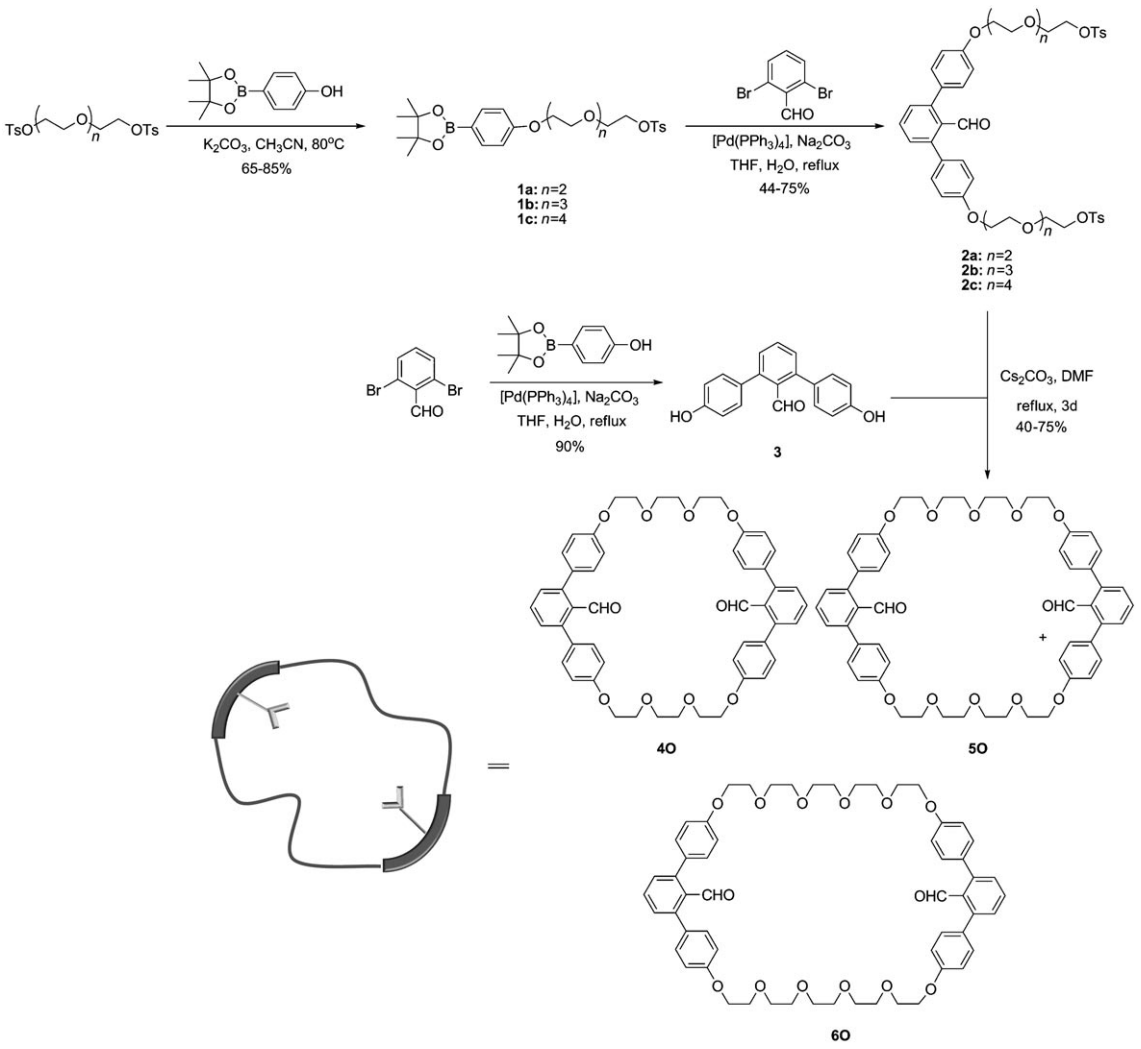
The term "self-sorting" has been discussed extensively in recent years. Usually, "sorting" is defined as a process in which different subunits are controlled with precise constitutional and/or positional order according to certain features or criteria. Thus "self-sorting" refers to not only the ability to distinguish "self" from "nonself", but also the operation completed simultaneously and orthogonally within the mixtures.[15] Intuitively, the more similar the subunits are, the more difficult self-sorting is, which is why self-sorting is very common in biological systems but rare in synthetic systems.[16] Here we demonstrate rapid and highly accurate self-sorting behaviors in a complex system, namely, a mixture of two macrocycles and two diamines. Although their reactive groups are completely the same, only two kinds of conformationally suitable aromatic diamine@macrocycle species are found. To the best of our knowledge, this is the first example of self-sorting inclusion behavior controlled by DCC. Our results provide a model system to mimic biochemical systems.

Results and Discussion

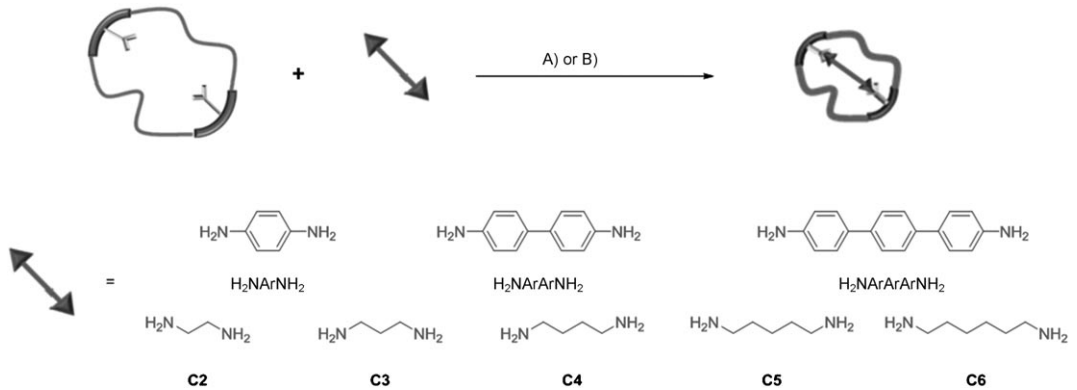
Synthesis of macrocycles 4O, 5O, and 6O, and formation of aromatic amines@macrocycles: Our target macrocycles **4O**, **5O**, and **6O** were designed to incorporate two 2,6-diphenylbenzaldehyde units and ethylene glycol fragments with variable chain length. Scheme 1 illustrates the synthetic approach to macrocycles **4O**, **5O**, and **6O**. α,ω-Bis-OTs ethylene glycols were prepared by a modified literature procedure[17] and subjected to nucleophilic reactions with 4-hydroxyphenylboronate to afford intermediates **1a**, **1b**, and **1c**. Compound **2a** was obtained by a Suzuki cross-coupling procedure between **1a** and 2,6-dibromobenzaldehyde in moderate yield. The same Suzuki cross-coupling reaction between **1a** and 4-hydroxyphenylboronate gave **3** in 90% yield. Compound **4O** was obtained by the ring-closing reactions of **2a** with **3** in highly dilute DMF solution in 75% yield. Following the same procedures, **5O** and **6O** were also obtained in moderate yields. These macrocyclic compounds are readily soluble in common organic solvents, such as toluene, THF, and CH_2Cl_2. The structures and purity of all new compounds were fully characterized and verified by ^1H and ^{13}C NMR spectroscopy, elemental analysis, and ESI HRMS.

The condensation step (Scheme 2) was performed by two procedures that differed in the amount of acid catalyst used. For aliphatic amines, procedure A was preferred: Only 0.1 equivalents of trifluoroacetic acid (TFA) were used, but a longer reaction time ($\approx$1 h) was used. Procedure B was used for aromatic amines by adding 100 equivalents of TFA and using a dramatically shorter reaction time (1 min), although, as shown in the literature, this is not the optimum method for establishing equilibrium.[18]

Several rigid aromatic amines with different length were first chosen to study the flexibility of **4O**, **5O**, and **6O**. Partial ^1H NMR spectra (300 MHz, $CDCl_3$, 298 K) of **4O** treated with three different linear aromatic amines are outlined in Figure 1. Under the conditions of procedure A for 1 h, the signal assigned to CHO at $\delta = 9.77$ ppm in the ^1H NMR spectrum of **4O** (Figure 1a) completely disappeared and a new signal assigned to the protons of imino groups (CH=N) emerged at $\delta = 8.33$ ppm (Figure 1b). This, combined with the fact that all signals assigned to aromatic protons of **4O** moved downfield and a new singlet appeared at $\delta =$ 6.96 ppm, indicated that a [1+1] bicyclic compound was formed in nearly quantitative yield on mixing **4O** with H_2NArNH_2.[19] Meanwhile, the ESI mass spectrum proved the formation of the proposed structure. Only an ion peak at *m/z* 881.4 for $[M+H]^+$ was observed. Moreover, as shown in Figure 1c, this reaction was went almost to completion without byproducts in only 1 min. The evenly downfield shifted signals could be assigned to the salt form of the Schiff bases. All characterization techniques verified the formation and the purity of the [1+1] intramolecular product, excluding the formation of any oligomers or polymers. Figure 1d illustrates the partial ^1H NMR spectrum when aniline was used instead of H_2NArNH_2. Apparently, because the mono-amine could not form such a chelate-type bicyclic product, clean ^1H NMR spectra were hard to achieve. The signals assigned to the imino groups split into two peaks due to formation of two different imines. Moreover, the signal assigned to CHO ($\delta = 9.42$ ppm) still existed, but it moved



Scheme 1. Synthetic approach to macrocyclic hosts **4O**, **5O**, and **6O**.



Scheme 2. Condensation reaction between macrocycles and diamines. Conditions: A) TFA (0.1 equiv), 1 h, 70 °C; B) TFA (100 equiv), 1 min, RT.

upfield owing to the addition of TFA. Based on the above facts, we speculate that the cavity size of **4O** is sufficient to accommodate a diamine with the length of phenyl and the second aldehyde is still available if the cavity is not fully filled.

With benzidine ($H_2NArArNH_2$), a white precipitate was immediately generated after the addition of 100 equivalents of TFA and the filtrate showed no clear ^{1}H NMR signals, with a few broad peaks indicating typical formation of oligomers or polymers. This indicated that this process was so

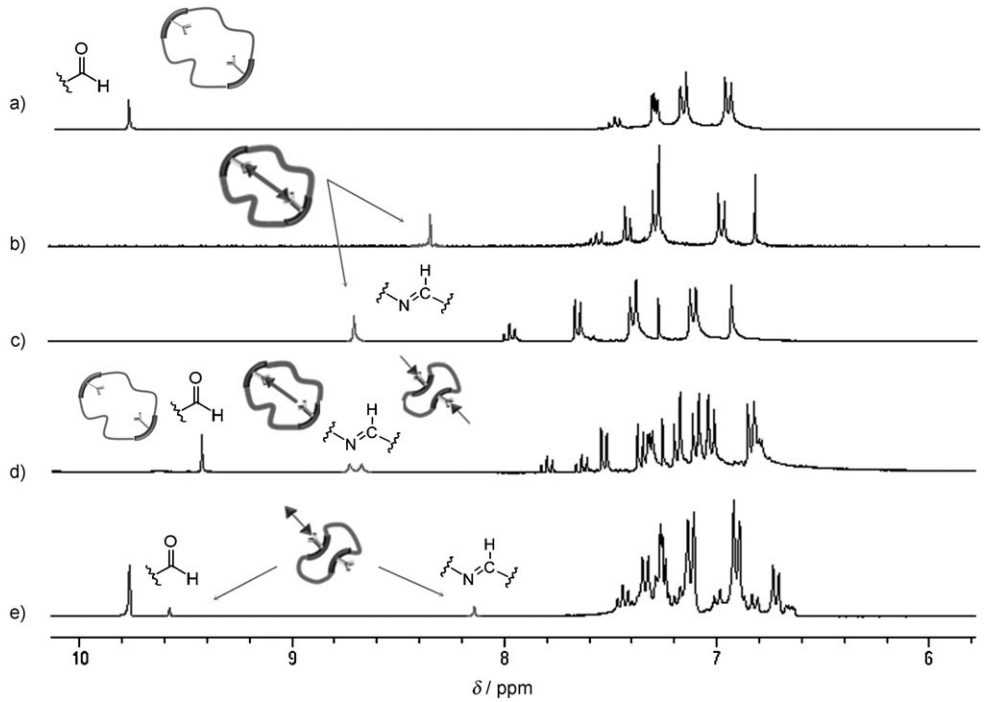
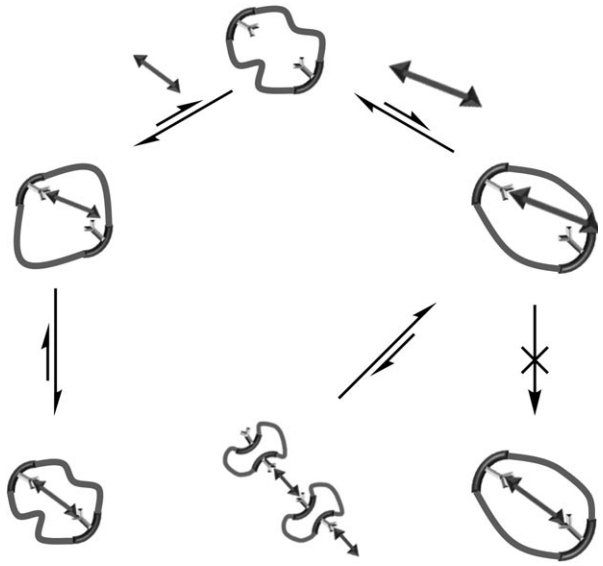


Figure 1. Partial ^{1}H NMR spectra (300 MHz, $CDCl_3$, 298 K) of a) **4O**, b) **4O** + H_2NArNH_2 (procedure A), c) **4O** + H_2NArNH_2 (procedure B), d) **4O** + $ArNH_2$ (procedure B), e) **4O** + $H_2NArArNH_2$ (procedure A). All compounds were in equimolar concentrations (1×10^{-2} mol L^{-1}).

quick that we could hardly observe the formation of any intermediates. Figure 1e illustrates the partial ^{1}H NMR spectrum, for which we simply combined the two reactants. The ^{1}H NMR spectrum revealed that the intermediate exhibits one signal assigned to CHO at $\delta = 9.58$ ppm and an imine signal at $\delta = 8.14$ ppm, with integral ratio of 1:1. Further comparison of aromatic protons revealed that Figure 1d corresponds to a mixture of the two starting materials and the mono-condensed intermediate with both a free aldehyde group and a free amino group. We speculated that $H_2NArArNH_2$ is too large to be contained inside the cavity of **4O**, so further intramolecular condensation was prevented. Therefore intermolecular reactions to give oligomers or polymers were preferred.

The different inclusion behavior of **4O** with various aromatic diamines is shown in Scheme 3, which is very similar to the typical protein–protein interaction process.[20] For short-chain diamines, the first imine bond is easily formed after a diffusional encounter, then the macrocycle reshapes its oligoethylene glycol chains to satisfy bonding of the second imine before formation of the final bonds. Self-adjustment of the flexible oligoethylene glycol chains and formation of the second imine bond can apparently considered as a single step because the rate is very fast. However, for a diamine with a long rigid chain, the energy for the conformational changes is too high to promote the guest's further inclusion, so oligomers and polymers are easily generated from these A_2 and B_2 systems.

Similar results were obtained with macrocycles **5O** or **6O** and various diamines. As shown in Figure 2, [1+1] bicyclic



Scheme 3. Inclusion behavior between **4O** and linear aromatic amines.

inclusion compounds of **5O** with aromatic diamines H_2NArNH_2 and $H_2NArArNH_2$ were obtained in quantitative yield. All protons were shifted downfield upon addition of TFA. Meanwhile, ESI-MS shows the ion peak of [1+1] addition products at m/z 969.4 for $[M+H]^+$. Compared with **4O**, **5O** could contain the longer rigid diamine $H_2NArArNH_2$ owing to the prolonged flexible ethylene glycol chain, which self-adjusted the size of the cavity and

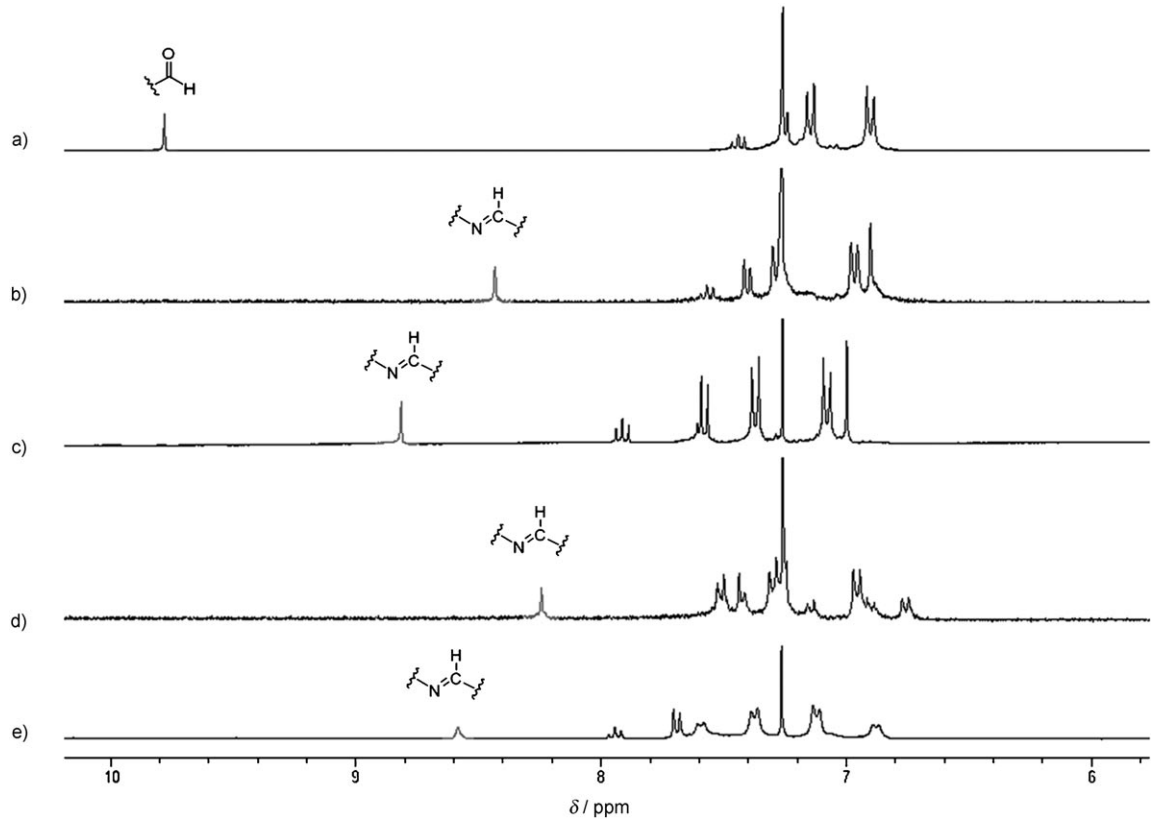


Figure 2. Partial ^{1}H NMR spectra (300 MHz, $CDCl_3$, 298 K) of a) **5O**, b) **5O** + H_2NArNH_2 (procedure A), c) **5O** + H_2NArNH_2 (procedure B), d) **5O** + $H_2NArArNH_2$ (procedure A), e) **5O** + $H_2NArArNH_2$ (procedure B). All compounds were in equimolar concentrations (4×10^{-3} mol L^{-1}).

the distance between the two formyl groups of **5O**. Once the condensation reaction was completed at one site, the intramolecular reaction was preferred to the intermolecular reaction in solution, and the [1+1] addition product was obtained regardless of the reaction time and the amount of TFA added. The same results were obtained with **6O** (Figure 3). Both ^{1}H NMR and ESI-MS spectra confirmed the production and purity of rigid diamines@**6O**. However, for 4,4″-diamino-*p*-terphenyl ($H_2NArArArNH_2$), the intramolecular reaction was prevented because the length of three phenyl groups was too long for **6O**. Therefore, the distance between the two formyl groups could not match the rigid rod no matter how the flexible chain was stretched (see the Supporting Information).

X-ray diffraction analysis of the single-crystal structure of H_2NArNH_2@**4O** and $H_2NArArNH_2$@**5O** led to further identification of [1+1] inclusion products. As shown in Figure 4, the diamine compounds are "stuck" in the cavity and the phenyl groups show small torsion angles to ensure good conjugation of the Schiff bases. Meanwhile, the ethylene glycol chains adopt the most stable helix form, with *trans-gauche-trans* conformation around the successive O-C-C-O bonds.[21] To sum up, rigid amines with various lengths react with **4O**, **5O**, and **6O** to give [1+1] inclusion compounds; however, only oligomers or polymers were obtained when the macrocycles were not large enough.

Study of flexible aliphatic amines@macrocycles: We further chose to use ethane-1,2-diamine (**C2**), propane-1,3-diamine (**C3**), butane-1,4-diamine (**C4**), pentane-1,5-diamine (**C5**), and hexane-1,6-diamine (**C6**) to understand the behavior of **4O**, **5O**, and **6O** when treated with flexible amines. Only intramolecular [1+1] addition products were obtained even though the lengths of the aliphatic amine in a stretched conformation were much longer than the distance between two aldehyde groups in the macrocycle hosts. For **4O**, for example, an equimolar solution of the macrocyclic host and aliphatic diamine guest in $CDCl_3$ showed almost unique aromatic protons, as illustrated in Figure 5. The signals assigned to imines were at $\delta = 8.11$ (**C2@4O**), 8.02 (**C3@4O**), 8.03 (**C4@4O**), 8.04 (**C5@4O**), and 7.96 ppm (**C6@4O**). The clean ^{1}H NMR spectra definitely indicated formation and the purity of intramolecular [1+1] addition products. We obtained similar results for larger macrocycles as well (see the Supporting Information). Therefore, if the diamine molecule is small, the host undergoes conformational readjustment to arrange its reactive sites to be complementary to the guest regardless of whether the diamines were flexible or not. However, relatively large and flexible diamine molecules can fold themselves to give intramolecular condensation products, whereas rigid ones give oligomers or polymers, as shown in Scheme 4.

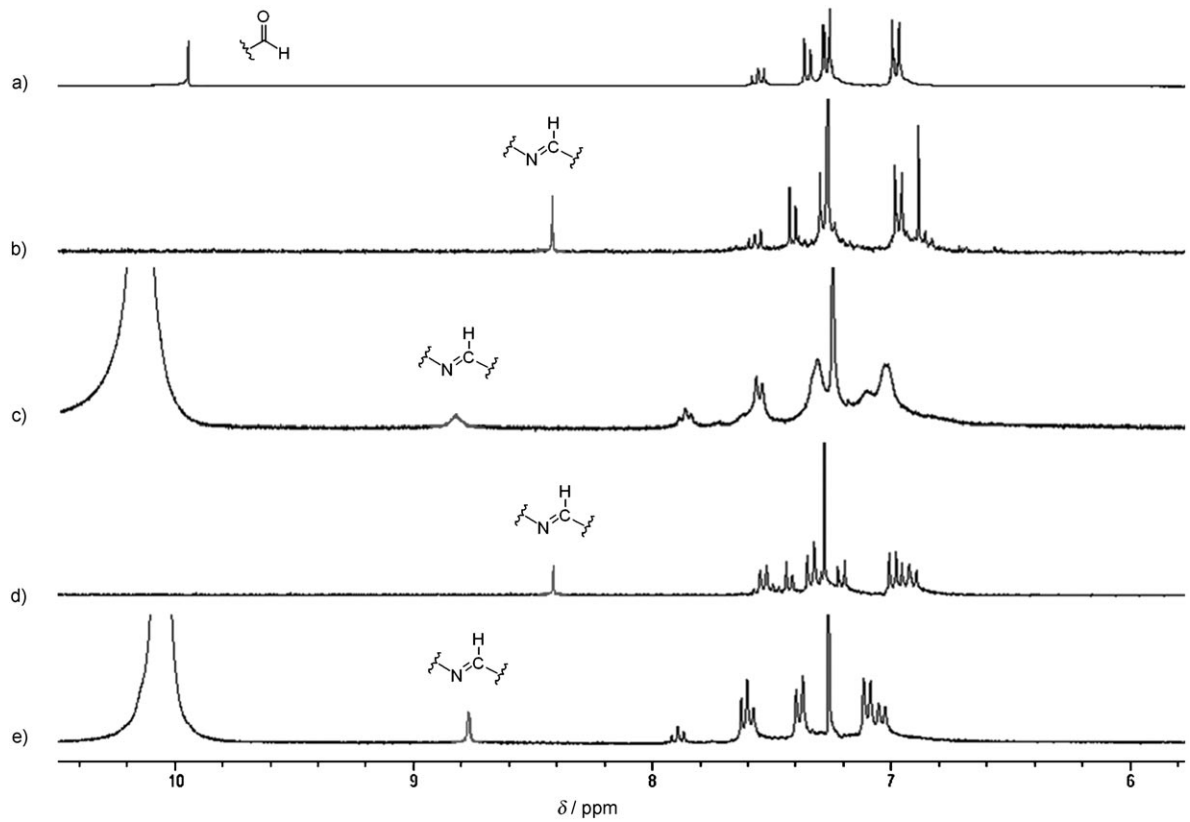


Figure 3. Partial ^{1}H NMR spectra (300 MHz, $CDCl_3$, 298 K) of a) **6O**, b) **6O** + H_2NArNH_2 (procedure A), c) **6O** + H_2NArNH_2 (procedure B), d) **6O** + $H_2NArArNH_2$ (procedure A), e) **6O** + $H_2NArArNH_2$ (procedure B). All compounds were in equimolar concentrations (4×10^{-3} mol L^{-1}).

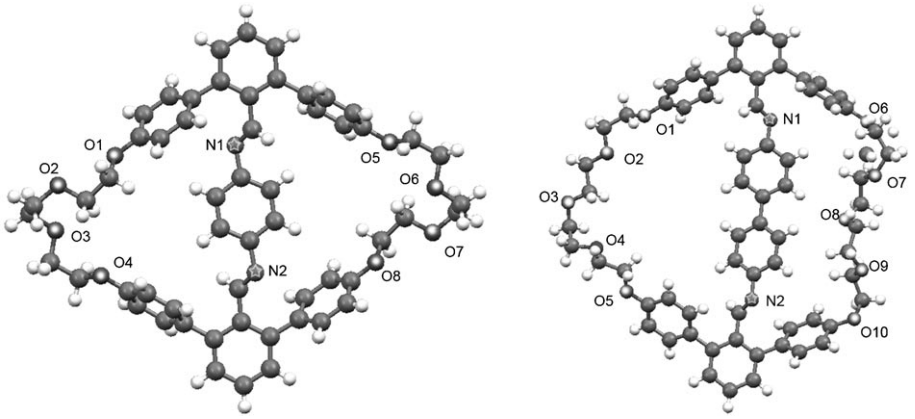


Figure 4. Single-crystal structures of H_2NArNH_2@**4O** (left) and $H_2NArArNH_2$@**5O** (right).

^{1}H NMR study of the reorganization ability of macrocycles: It is interesting to examine what would happen if several amines and a macrocycle were mixed in solution. To answer this question, four typical amines were selected: aniline, **C2** (representing flexible diamines), H_2NArNH_2, and $H_2NArArNH_2$ (representing short and long rigid aromatic diamines, respectively). Before the experiment, it might be argued that these systems would be under kinetic control. For example, **C2** might be more reactive because of its strong nucleophilicity. To exclude this possibility, we chose procedure A as the experimental conditions under which both nucleophilic and less nucleophilic amines undergo a fast condensation reaction. Figure 6a illustrates ^{1}H NMR spectra of **4O** reacting with four different aliphatic amines. It could be concluded that H_2NArNH_2@**4O** was the major product in the mixture, but the broadness of the signals indicated that other condensation products were also present. However, these byproducts gradually vanished after heating at 70 °C for 1 h. The sharp singlet at $\delta = 8.70$ ppm, together with other aromatic protons that perfectly match those in Figure 6b, definitely showed that H_2NArNH_2@**4O** was the dominant species in the mixture, whereas other unconsumed amines finally became insoluble ammonium salts.

In summary, rigid aromatic amines with suitable lengths are the most favorable candidates to be incorporated into the cavity of the macrocycle. First, compared with aniline, the aromatic diamines could form a "chelate-like" structure,

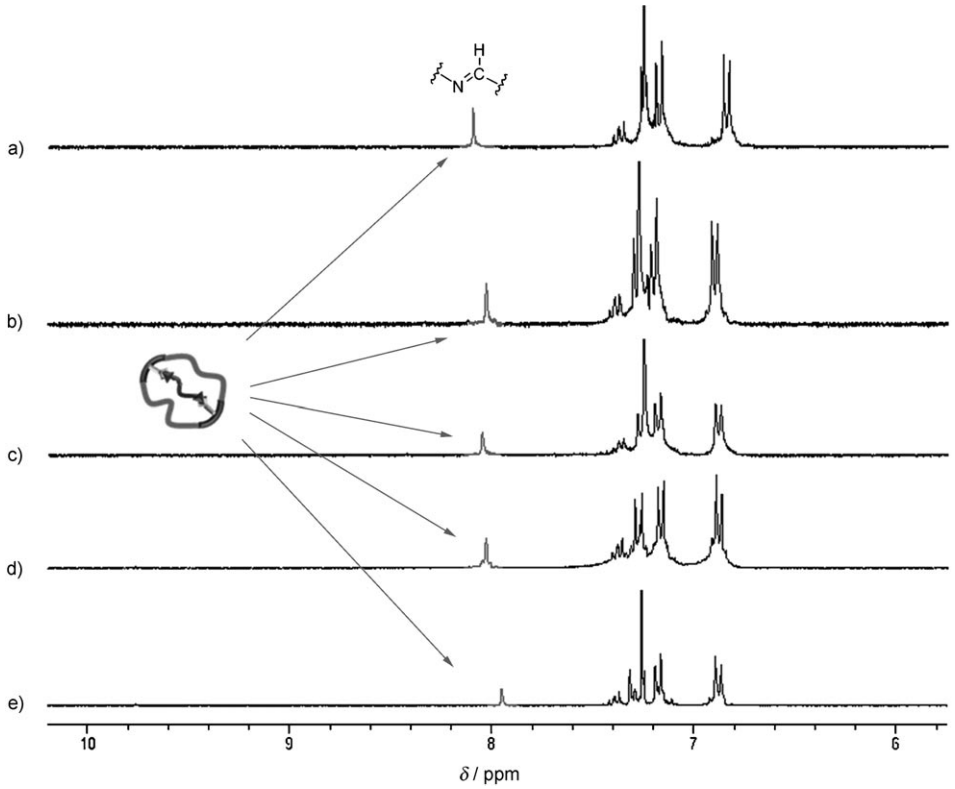
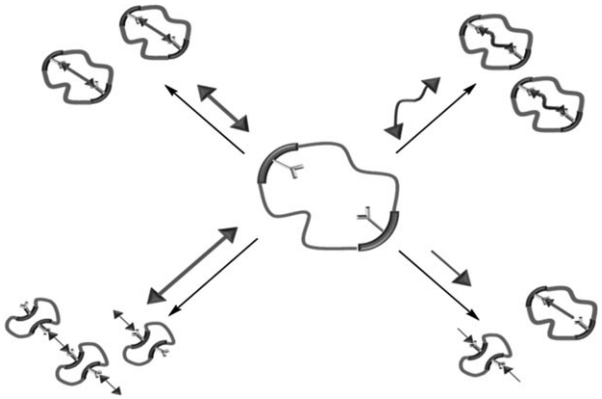


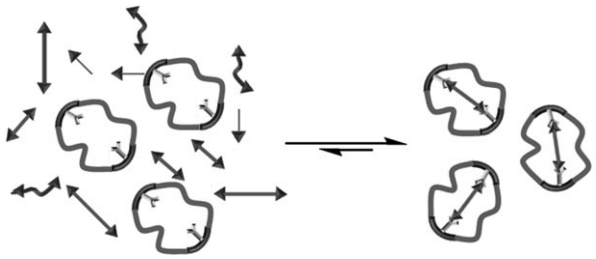
Figure 5. ^{1}H NMR spectra (300 MHz, $CDCl_3$, 298 K) of **4O** treated with five different linear aliphatic amines: a) **4O**+**C2**, b) **4O**+**C3**, c) **4O**+**C4**, d) **4O**+**C5**, e) **4O**+**C6**. All compounds were in equimolar concentrations (2×10^{-3} mol L^{-1}).



Scheme 4. Inclusion behavior between **4O** and linear aliphatic and aromatic amines.

which is thermodynamically much more favorable due to the large energy gain on the formation of an additional bond. Secondly, the formation of oligomers or polymers between $H_2NArArNH_2$ and **4O** was prevented by a large entropy loss. As a result, the most stable, highly conjugated H_2NArNH_2@**4O** formed instead of the nonconjugated **C2**@**4O** (Scheme 5).

Static study of self-sorting behavior: With the above results in hand, we mixed different macrocycles and mixtures of diamines to investigate whether the system is able to sort suitable diamines. Surprisingly, these flexible hosts also showed an excellent self-sorting ability, as usually observed in noncovalent systems. At first, condensation occurred immediately upon addition of 100.0 equivalents of TFA to an equimolar mixture of **4O**, **6O**, H_2NArNH_2, and $H_2NArArNH_2$ in $CDCl_3$, as indicated by ^{1}H NMR spectroscopy. As is characteristic of the incorporation of amines into macrocycles, three sets of imine protons appeared at $\delta=8.84$, 8.77, and 8.73 ppm, indicating that the mixture contained the salt forms of the Schiff bases H_2NArNH_2@**6O**, $H_2NArArNH_2$@**6O**, and H_2NArNH_2@**4O**, respectively. This result was confirmed by ESI-MS as well: peaks at *m/z* 881.4, 1057.5, 1093.5, and 1169.5, assigned to $[H_2NArNH_2$@**4O**$+H]^+$, $[H_2NArNH_2$@**6O**$+H]^+$, $[H_2NArNH_2$@**6O**$+2H_2O]^+$, and $[H_2NArArNH_2$@**6O**$+2H_2O]^+$, respectively, were found. The ratio of matched pairs and mismatched pairs was estimated to be more than 90:10 from the integrated intensity of the imine protons, which further proved that rigid aromatic amines of suitable length are the most favorable candidates for incorporation into the cavity of the macrocycle: **4O** matched with H_2NArNH_2, and **6O** with $H_2NArArNH_2$. This rapid and highly accurate self-sorting behavior is remarkable in an artificial system. Inevitably, because of the flexibility of the **6O** macrocycle, mismatched H_2NArNH_2@**6O** was also obtained as minor product after rapid conformational readjustment. However, according to the principle of DCC, these less stable products, or mismatched pairs, would finally transform into more stable products after a so-called error-check process. After heating



Scheme 5. Inclusion behavior between **4O** and four amines.

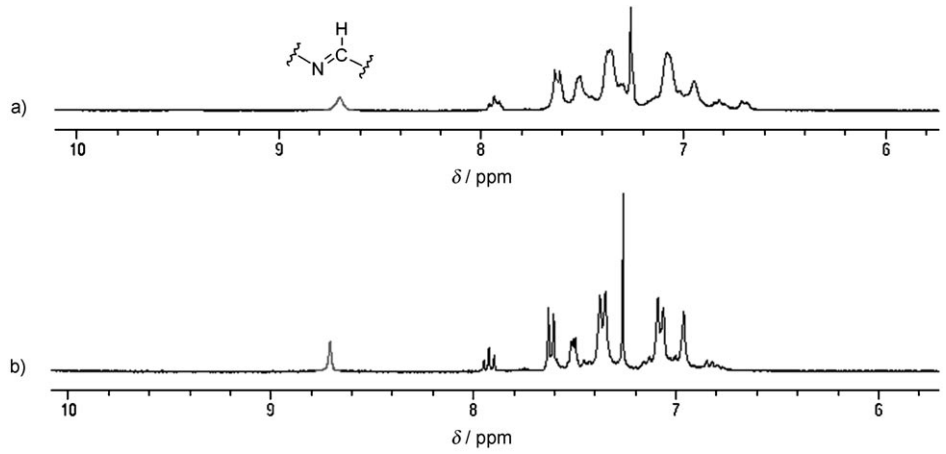


Figure 6. Partial ^{1}H NMR spectra (300 MHz, $CDCl_3$, 298 K) of a mixture of **4O**, aniline, ethane-1,2-diamine, 1,4-diaminobenzene, and benzidine in the presence of TFA (100 equiv) after a) 1 min and b) 1 h. All compounds were in equimolar concentrations (4×10^{-3} mol L^{-1}).

for 1 h, the matched pairs of $H_2NArArNH_2$@**6O** and H_2NArNH_2@**4O** were finally obtained in nearly quantitative yield (Figure 7b).

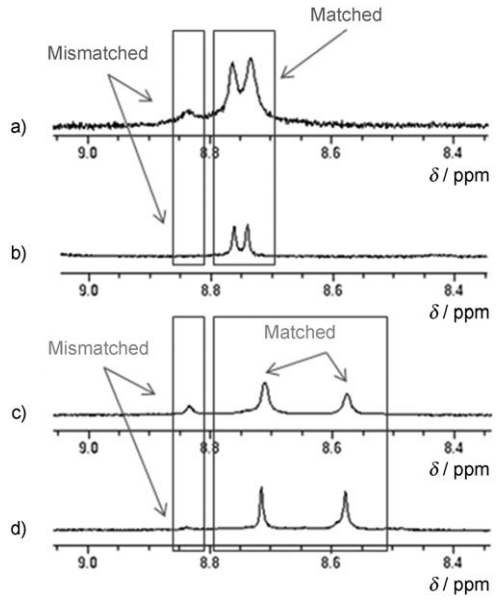
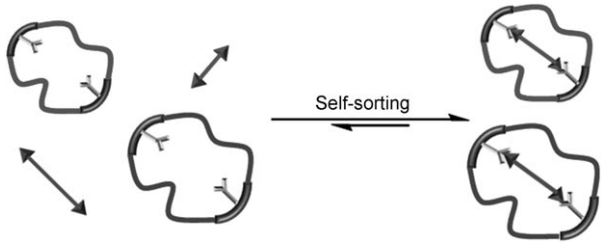


Figure 7. Partial ^{1}H NMR spectra (300 MHz, $CDCl_3$, 298 K) of a mixture of **4O**, **6O**, H_2NArNH_2, and $H_2NArArNH_2$ in the presence of TFA (100 equiv) after a) 1 min and b) 1 h, and of a mixture of **4O**, **5O**, H_2NArNH_2, and $H_2NArArNH_2$ in the presence of TFA (100 equiv) after c) 1 min and d) 1 h. All compounds were in equimolar concentrations (4×10^{-3} mol L^{-1}).

We can then conclude that both kinetic and thermodynamic self-sorting behaviors could be observed on a very short timescale with high efficiency.[22] In this case, the thermodynamic product is also the kinetically favorable one, and complete equilibrium can be reached after heating with exclusion of mismatched products thanks to the inherent "proof-reading" ability of DCC. Even when the macrocycles are of very similar size, such as **4O** and **5O**, self-sorting still proceeds efficiently (Scheme 6). Similarly, a mixture of matched and mismatched components was obtained initially, but the imine signals at $\delta=8.83$ ppm assigned to H_2NArNH_2@**5O** in Figure 7c decreased dramatically after 1 h of heating, and only H_2NArNH_2@**4O** and $H_2NArArNH_2$@**5O** were produced, as evidenced by the signals at $\delta=$ 8.71 and 8.58 ppm, respectively (Figure 7d). Meanwhile, ESI-MS provided further confirmation of the proposed structures: peaks at *m/z* 881.4, 969.4, and



Scheme 6. Self-sorting behavior.

1081.5, assigned to $[H_2NArNH_2$@**4O**$+H]^+$, $[H_2NArNH_2$@**5O**$+H]^+$, and $[H_2NArArNH_2$@**5O**$+2H_2O]^+$, repectively, were found.

Time-dependent ^{1}H NMR study of self-sorting behavior: Figure 8 shows time-dependent ^{1}H NMR spectra of a mixture of **4O**, **6O**, H_2NArNH_2, and $H_2NArArNH_2$ in $CDCl_3$ at 348 K. The signals of formyl protons at $\delta=9.83$ and 9.76 ppm appeared, and finally all signals of formyl protons disappeared over time. As the ^{1}H NMR spectra show, there are only two signals, which means that no intermediates are formed other than inclusion products. Thus, we confirmed that formation of the imine bonds is a self-accelerating process. After one imine bond is formed, the reaction rate of the other bond becomes much faster, even though the reactivity of the second amino group dramatically drops after the end of condensation of the first one.[23] In addition, the formyl protons assigned to **6O** at $\delta=9.76$ ppm decreased faster than those of **4O**, probably because **6O** could react with both H_2NArNH_2 and $H_2NArArNH_2$ with similar rates, whereas the reaction rate between **4O** and $H_2NArArNH_2$ was relatively slow, as shown before. As a result, "wrong" structures are unavoidable, so the chemical shift assigned to dynamic mismatched product H_2NArNH_2@**6O** at $\delta=$ 8.32 ppm persists for the first 15 min. However, this peak then gradually vanished over 1 h, which indicates that the

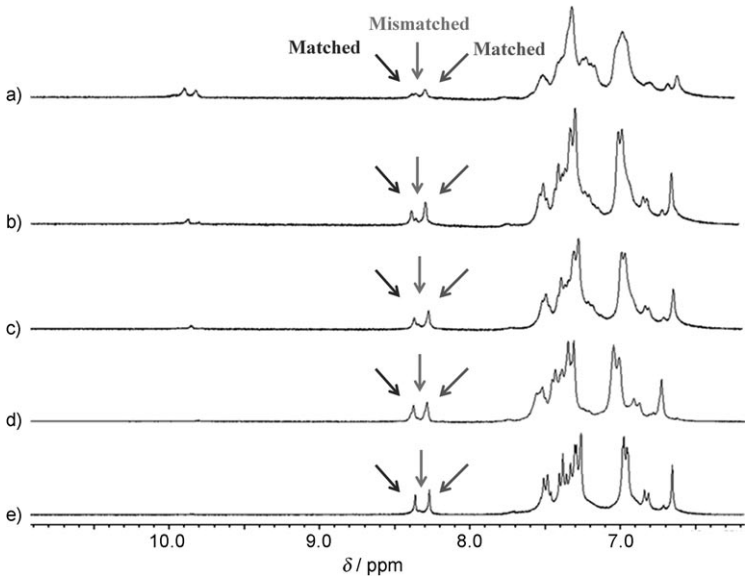


Figure 8. Time-dependent partial ^{1}H NMR spectra (300 MHz, $CDCl_3$, 348 K) of self-sorting behavior of a mixture of **4O**, **6O**, H_2NArNH_2, and $H_2NArArNH_2$ in the presence of TFA (0.1 equiv) after a) 5, b) 10, c) 15, d) 45, and e) 60 min. All compounds were in equimolar concentrations (1×10^{-2} mol L^{-1}).

flexible smart macrocycles undergo error-correction steps to adjust their conformation and accommodate the most suitable guests, that is, to distinguish "self" from "nonself". Finally, the clean signals assigned to thermodynamically controlled products $H_2NArArNH_2$@**6O** and H_2NArNH_2@**4O** at $\delta = 8.36$ and 8.27 ppm indicate that the reaction of the dynamic product, either H_2NArNH_2@**6O** or proposed oligomers generated by **4O** and $H_2NArArNH_2$, is reversible, and equilibrium is established to afford the most stable self-sorted products. Although the imine bonds are the same, only the conformationally flexible side chains control the final equilibrium state, which further confirms our induced-fit hypothesis.

Theoretical explanation of self-sorting: To understand the origin of selectivity and how the flexible chains of macrocycles control the self-sorting behavior by the induced-fit principle, theoretical calculations were performed by using Gaussian 03.[24] Geometry optimization and single-point energy (SPE) calculations were done at the B3LYP/6-31G(d) level (ZPE correction parameter: 0.9804) and calculations of solvent SPEs were based on the optimized gas-phase geometry by using the CPCM model. Besides the proposed structures of macrocycles and their relevant inclusion compounds, model compounds without oligo(ethylene glycol) units were optimized as well (Figure 9). In-depth understanding of the process was gained by calculation of enthalpies (Table 1).[25]

The enthalpy contribution can be roughly divided into two parts: 1) imine bond formation and 2) conformational change of ethylene glycol. Although sizes are quite different for these macrocycles and diamines, the reaction activities for both aldehyde groups and amino groups are almost the same. Therefore, model compound **M** served as a reference to study the effects of imine bond formation, and the energies of condensation are relatively close: 15.4 kcal mol^{-1} for H_2NArNH_2@**M** and 20.3 kcal mol^{-1} for $H_2NArArNH_2$@**M**. These results also indicate the reversible nature of imine formation.

Similar results were obtained on calculating **6O** and its relatives (Figure 10). The enthalpy changes of condensation are 19.4 kcal mol^{-1} for H_2NArNH_2@**6O** and 21.8 kcal mol^{-1} for $H_2NArArNH_2$@**6O**, and solvent SPEs were calculated as 20.2 and 21.8 kcal mol^{-1}, respectively. We can then conclude that for small diamines, the enthalpy contribution of oligo(ethylene glycol) conformational changes is very small, so that only slight increases are observed. However, when we turned to **4O** and its derivatives, only the H_2NArNH_2@**4O** system showed the similar enthalpy changes both in vacuum and in solution. The $H_2NArArNH_2$@**4O** system exhibits a very high enthalpy change of 27.2 kcal mol^{-1} in vacuum or 31.0 kcal mol^{-1} in solution, which means the enthalpy penalty comes mainly from the oligo(ethylene glycol) chains stretching. In the H_2NArNH_2@**4O** system, the macrocycle is large enough to accommodate H_2NArNH_2 inside the cavity,

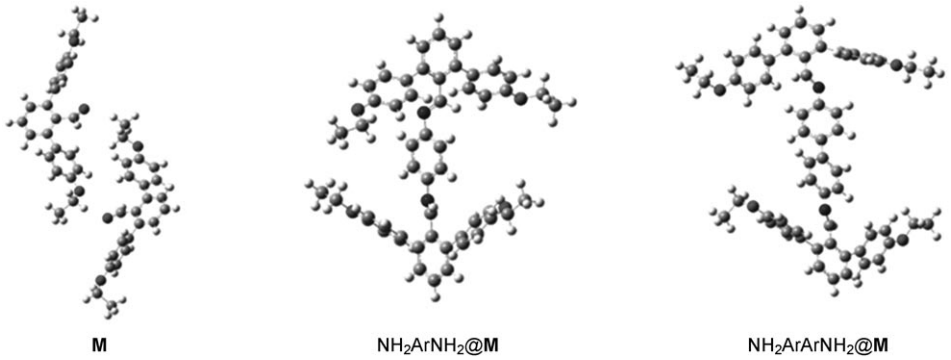


Figure 9. Computed structures of model imine intermediates.

Table 1. Calculated reaction enthalpies of condensation.

Compound	ΔH_{gas} [kcal mol^{-1}]	ΔH_{sol} [kcal mol^{-1}]
H_2NArNH_2@**4O**	15.8	18.0
$H_2NArArNH_2$@**4O**	27.2	31.0
H_2NArNH_2@**5O**	17.1	22.4
$H_2NArArNH_2$@**5O**	20.4	23.9
H_2NArNH_2@**6O**	19.4	20.2
$H_2NArArNH_2$@**6O**	21.8	21.8
H_2NArNH_2@**M**	15.4	–
$H_2NArArNH_2$@**M**	20.3	–

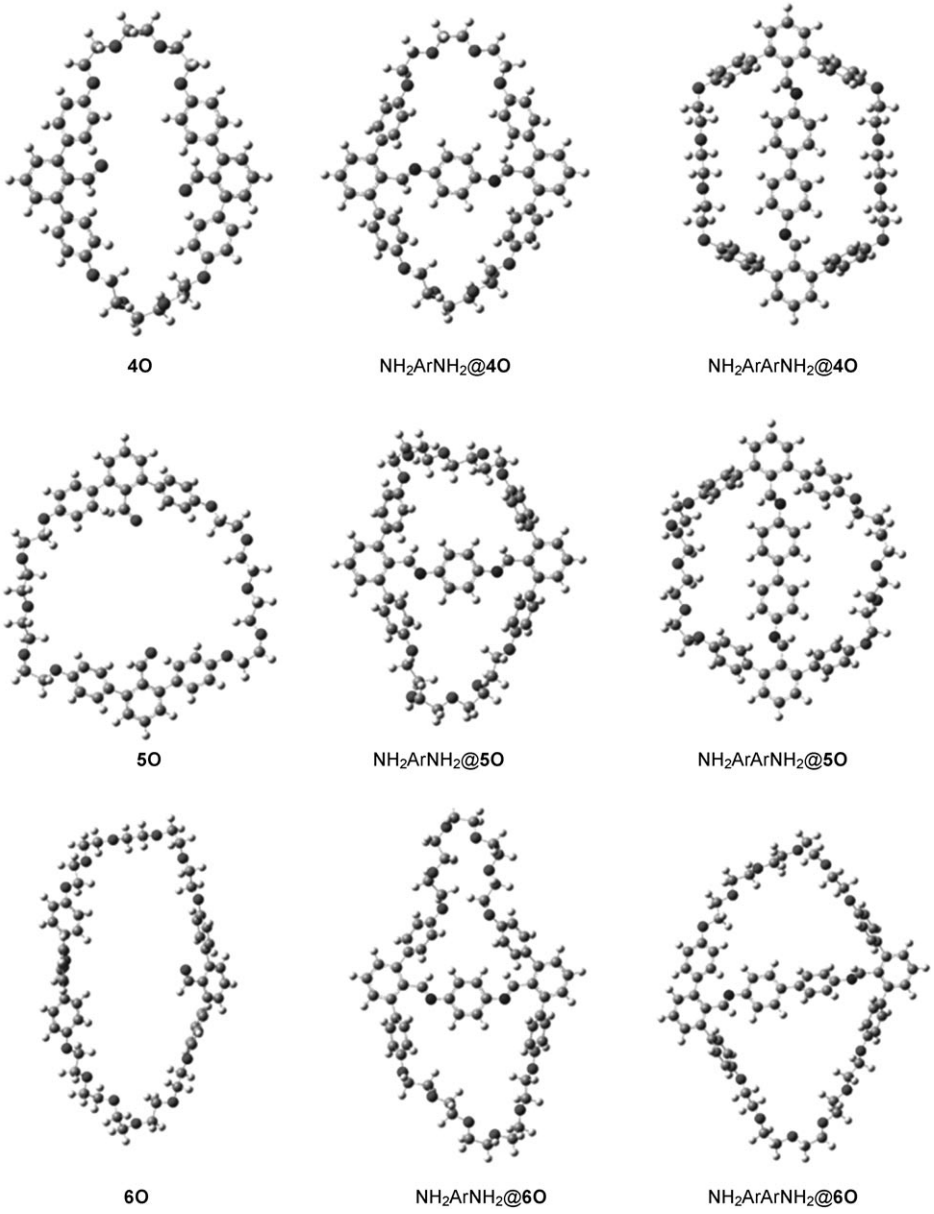


Figure 10. Computed structures of **4O**, **5O**, **6O**, and their imine intermediates.

and the structure was similar to the most stable *trans-gauche-trans* conformation, in accordance with the previous single-crystal data. However, in the $H_2NArArNH_2$@**4O** system, if the rigid diamine is incorporated into the cavity, all oligo(ethylene glycol) chains are forced to be nearly linear, so that the repulsion of the flexible chains dominates the enthalpy contribution to prevent the generation of $H_2NArArNH_2$@**4O**.

Because product formation occurs under thermodynamic control, product distributions depend only on the relative stabilities of the final products. It is speculated that in the mixture of **4O**, **6O**, H_2NArNH_2, and $H_2NArArNH_2$ in the presence of TFA, the enthalpy contribution of oligo(ethylene glycol) conformational changes is very similar between H_2NArNH_2@**6O** and $H_2NArArNH_2$@**6O**, so both inclusion compounds are observed. However, because $H_2NArArNH_2$@**4O** is not a thermodynamically favored product, only H_2NArNH_2@**4O** is formed, and $H_2NArArNH_2$@**6O** is "forced" to transform into H_2NArNH_2@**6O**, by virtue of reversible DCC reaction. Finally, the high enthalpy demand of $H_2NArArNH_2$@**4O** is the key element to ensure that self-sorting can complete with high accuracy in a short time.

Conclusion

In summary, we have developed a series of "smart" macrocycles, **4O**, **5O**, and **6O**, for self-sorting the various diamines that fit them by DCC. The investigations of their condensation properties with different amines indicate that although they have nearly the same structure except for the different side-chain lengths, they exhibit rapid and highly accurate self-sorting behaviors. The cavity limit together with the flexible side chains allow the macrocycles to "intelligently" recognize conformationally suitable aromatic diamines through the induced-fit principle. The self-sorting behaviors of both **4O**–**5O** and **4O**–**6O** systems are controlled by either kinetic or thermodynamic conditions. Taking **4O**–**6O**, for example, two bicyclic compounds H_2NArNH_2@**4O** and $H_2NArArNH_2$@**6O** are formed as major products immediately after an excess of acid is added, and the self-sorting effects are enhanced after heating. Time-dependent ^{1}H NMR analyses indicate that multivalent bonds of these cooporations between aldehydes and amines can be facilely and effectively constructed simultaneously. In the mixed DCC process, the matched pairs are the main products not only under thermodynamic control, but also under kinetic control. Theoretical calculation shows the large enthalpy change of $H_2NArArNH_2$@**4O** may be the driving force.

The DCC concept is known for its "error-checking" nature. Our results demonstrate that although our "smart" molecules make errors at first, they find their partners in the end. Side-chain conformational readjustment is the key

to self-sorting, which is common in nature but rare in synthetic systems. This work helps to shed more light on the nature of molecular recognition and selectivity. Furthermore, such a covalent approach to synthesizing interlocked structures, such as rotaxanes[26] and catenanes,[27] is very difficult and examples are rare; a key reason for this is that a bicyclic inclusion structure that is easy to build and to break is hard to achieve. Finally, our systems may afford unique insights into the formation process of DCC-based rotaxanes and catenanes. The development of even "smarter" systems is in progress.

Experimental Section

General methods: Commercial chemicals were used as received. All air- and water-sensitive reactions were performed under a nitrogen atmosphere. ^{1}H and ^{13}C NMR spectra were recorded by using a Mercury Plus 300 MHz at RT or 70 °C in appropriate deuterated solvents. All chemical shifts are reported in parts per million (ppm); ESI HRMS spectra were recorded on a Bruker Apex IV FTMS. X-ray diffraction was performed by using a Bruker SMART-1000 diffractometer.

General procedure for the preparation of 1a, 1b, and 1c: A mixture of an oligo(ethylene glycol) bis-toluenesulfonate (27.3 mmol), (4-hydroxyphenyl)boronate pinacol ester (9.09 mmol), $[Pd(PPh_3)_4]$, and K_2CO_3 (13.6 mmol) in acetonitrile (200 mL) was heated at reflux overnight under nitrogen. After filtration, the solvents were removed under reduced pressure to afford crude product. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate 1:1) to afford the desired product.

Compound ***1a***: Colorless oil (yield: 85%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.78–7.80 (d, J = 8.1 Hz, 2H), 7.72–7.75 (d, J = 8.7 Hz, 2H), 7.31–7.33 (d, J = 8.1 Hz, 2H), 6.88–6.90 (d, J = 8.7 Hz, 2H), 4.11–4.17 (m, 4H), 3.80–3.83 (m, 2H), 3.60–3.70 (m, 6H), 2.42 (s, 3H), 1.33 ppm (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 163.9, 161.2, 144.7, 136.4, 132.9, 129.8, 127.9, 113.9, 83.5, 70.7, 69.6, 69.2, 68.6, 67.1, 24.8, 21.6 ppm; ESI-HRMS: m/z calcd for $C_{25}H_{35}BNaO_8S$: 529.2042; found: 529.2038 $[M+Na]^+$.

Compound ***1b***: Colorless oil (yield: 77%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.78–7.81 (d, J = 8.4 Hz, 2H), 7.72–7.75 (d, J = 8.7 Hz, 2H), 7.32–7.34 (d, J = 8.4 Hz, 2H), 6.88–6.91 (d, J = 8.7 Hz, 2H), 4.13–4.16 (m, 4H), 3.83–3.85 (m, 2H), 3.58–3.71 (m, 10H), 2.43 (s, 3H), 1.33 ppm (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 161.3, 161.2, 144.7, 136.4, 132.9, 129.8, 127.9, 113.9, 83.5, 70.7, 70.6, 69.6, 69.2, 68.6, 67.1, 24.8, 21.6 ppm; ESI-HRMS: m/z calcd for $C_{27}H_{39}BO_9S$: 551.2485; found: 551.2483 $[M+H]^+$.

Compound ***1c***: Colorless oil (yield: 65%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.78–7.81 (d, J = 8.4 Hz, 2H), 7.72–7.75 (d, J = 8.7 Hz, 2H), 7.32–7.35 (d, J = 8.4 Hz, 2H), 6.88–6.91 (d, J = 8.7 Hz, 2H), 4.13–4.17 (m, 4H), 3.85–3.87 (m, 2H), 3.58–3.71 (m, 14H), 2.44 (s, 3H), 1.33 ppm (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 160.9, 161.2, 144.8, 136.0, 132.5, 129.4, 127.5, 113.4, 83.1, 70.3, 70.1, 69.1, 68.9, 68.1, 66.7, 24.5, 21.2 ppm; ESI-HRMS: m/z calcd for $C_{29}H_{43}BO_{10}S$: 595.2748; found: 595.2738 $[M+H]^+$.

General procedure for the preparation of 2a, 2b, and 2c: A mixture of 2,6-dibromobenzaldehyde (1.73 mmol), boronic ester **1a**, **1b**, or **1c**, Na_2CO_3 (2 M, 6.90 mmol), and $[Pd(PPh_3)_4]$ (0.173 mmol) in THF (50 mL) and deionized water (5 mL) was heated at reflux overnight under nitrogen. The mixture was extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$. After removal of solvent under reduced pressure, the residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate 1:2) to afford the desired product.

Compound ***2a***: Yellow oil (yield: 75%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.93 (s, 1H), 7.79–7.82 (d, J = 8.4 Hz, 2H), 7.52–7.55 (t, J = 7.2 Hz, 1H), 7.32–7.36 (m, 6H), 7.25–7.28 (d, J = 8.7 Hz, 4H), 6.95–6.98 (d, J = 8.4 Hz, 4H), 4.14–4.19 (m, 8H), 3.84–3.87 (m, 4H), 3.62–3.72 (m, 12H), 2.43 ppm (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 193.9, 158.4, 144.8, 143.79, 133.1, 132.9, 132.0, 131.4, 130.8, 130.1, 129.8, 127.9, 114.2, 70.7, 69.7, 69.2, 68.7, 67.4, 21.6 ppm; ESI-HRMS: m/z calcd for $C_{45}H_{54}NO_{13}S_2$: 880.3031; found: 880.3025 $[M+NH_4]^+$.

Compound ***2b***: Yellow oil (yield: 59%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.93 (s, 1H), 7.78–7.81 (d, J = 8.4 Hz, 2H), 7.53–7.55 (t, J = 7.5 Hz, 1H), 7.32–7.36 (m, 6H), 7.25–7.28 (d, J = 8.7 Hz, 4H), 6.95–6.98 (d, J = 8.4 Hz, 4H), 4.14–4.19 (m, 8H), 3.86–3.90 (m, 4H), 3.60–3.75 (m, 20H), 2.44 ppm (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): δ = 193.9, 158.5, 144.8, 143.9, 133.2, 133.0, 132.1, 131.4, 130.8, 130.1, 129.8, 127.9, 114.2, 70.8, 70.7, 70.7, 70.6, 69.7, 69.2, 68.7, 67.4, 21.6; ESI-HRMS m/z: calcd for $C_{49}H_{59}O_{15}S_2$: 951.3290; found: 951.3284 $[M+H]^+$.

Compound ***2c***: Yield: 44%, yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.93 (1H, s), 7.78–7.81 (2H, d, J = 8.4 Hz), 7.53–7.55 (1H, t, J = 7.5 Hz), 7.32–7.36 (6H, m), 7.25–7.28 (4H, d, J = 8.7 Hz), 6.95–6.98 (4H, d, J = 8.4 Hz), 4.14–4.19 (8H, m), 3.86–3.90 (4H, m), 3.60–3.75 (20H, m), 2.44 (6H, s); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 194.0, 158.4, 144.8, 143.8, 133.1, 132.7, 131.9, 131.5, 130.8, 130.1, 129.8, 127.9, 70.8, 70.5, 69.6, 69.2, 68.6, 67.3, 21.6 ppm; ESI-HRMS: m/z calcd for $C_{53}H_{67}O_{17}S_2$: 1039.3814; found: 1039.3824 $[M+H]^+$.

Compound 3: A mixture of 2,6-dibromobenzaldehyde (0.778 g, 2.95 mmol), (4-hydroxyphenyl)boronate pinacol ester (2.00 g, 8.85 mmol), Na_2CO_3 (2 M, 3.12 g, 29.5 mmol), and $[Pd(PPh_3)_4]$ (0.340 g, 0.295 mmol) in THF (50 mL) and deionized water (18 mL) was heated at reflux overnight under nitrogen. The mixture was extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$. After removal of solvent under reduced pressure, the residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate 2:1) to afford **3** (0.80 g) as a white solid (yield 90%). ^{1}H NMR (CD_3COCD_3, 300 MHz): δ = 9.96 (s, 1H), 8.63 (s, 2H), 7.56–7.61 (t, J = 7.5 Hz, 1H), 7.33–7.35 (d, J = 7.5 Hz, 2H), 7.18–7.22 (d, J = 8.7 Hz, 4H), 6.89–6.94 ppm (d, J = 8.4 Hz, 4H); ^{13}C NMR (CD_3COCD_3, 75 MHz): δ = 195.0, 158.8, 145.3, 135.5, 132.9, 132.6, 131.3, 116.6 ppm; ESI-HRMS: m/z calcd for $C_{19}H_{15}O_3$: 291.1016; found: 291.1014 $[M+H]^+$.

General procedure for preparation of 4O, 5O, and 6O: A mixture of **3** (0.096 mmol), and **2a**, **2b**, or **2c** (0.096 mmol), Cs_2CO_3 (0.288 mmol) in DMF (100 mL) was heating at 100 °C for 2 d under nitrogen. After filtration, the solution was concentrated under reduced pressure to afford residues, which were purified by column chromatography (eluent: ethyl acetate) to afford the desired products.

Compound ***4O***: White solid (yield: 75%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.77 (s, 2H), 7.43–7.48 (t, J = 7.5 Hz, 2H), 7.25–7.27 (d, J = 7.5 Hz, 4H), 7.11–7.14 (d, J = 8.7 Hz, 8H), 6.90–6.93 (d, J = 8.4 Hz, 8H), 4.09–4.17 (m, 8H), 3.89–3.92 (m, 8H), 3.78 ppm (s, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 193.7, 158.2, 143.7, 133.3, 131.9, 131.1, 130.8, 129.8, 114.4, 71.0, 69.7, 67.6 ppm; ESI-HRMS: m/z calcd for $C_{50}H_{48}NaO_{10}$: 831.3140; found: 831.3129 $[M+Na]^+$.

Compound ***5O***: White solid (yield: 47%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.79 (s, 2H), 7.42–7.47 (t, J = 7.5 Hz, 2H), 7.24–7.26 (m, 4H), 7.14–7.16 (d, J = 8.7 Hz, 8H), 6.89–6.92 (d, J = 8.4 Hz, 8H), 4.12–4.15 (m, 8H), 3.89–3.92 (m, 8H), 3.74–3.77 ppm (m, 16H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 193.6, 158.3, 143.6, 133.0, 131.8, 131.2, 130.7, 129.8, 114.1, 70.7, 69.6, 67.4 ppm; ESI-HRMS: m/z calcd for $C_{54}H_{56}NaO_{12}$: 919.3664; found: 919.3655 $[M+Na]^+$.

Compound ***6O***: White solid (yield: 40%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.85 (s, 1H), 7.44–7.49 (t, J = 7.5 Hz, 2H), 7.27–7.29 (d, J = 7.5 Hz, 4H), 7.17–7.20 (d, J = 8.7 Hz, 8H), 6.91–6.94 (d, J = 8.4 Hz, 8H), 4.15 (m, 8H), 3.87 (m, 8H), 3.69–3.72 ppm (m, 24H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 193.7, 158.5, 143.8, 133.3, 132.0, 131.3, 130.8, 130.0, 114.3, 70.9, 70.7, 69.7, 67.5 ppm; ESI-HRMS: m/z calcd for $C_{58}H_{64}NaO_{14}$: 1007.4188; found: 1007.4172 $[M+Na]^+$.

General procedure for preparation of single crystals of H_2NArNH_2@4O and $H_2NArArNH_2$@5O: A phase-separation process was employed to obtain single crystals. A mixture of macrocycle (0.002 mmol) and aromatic diamine (0.002 mmol) was dissolved in $CHCl_3$ (1 mL) and TFA (15 μL) was injected before MeOH (2 mL) was added. One week later, colorless crystals were finally collected from the mixture.

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