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Composition- and Size-Controlled Cyclic Self-Assembly by Solvent- and C_{60}-Responsive Self-Sorting

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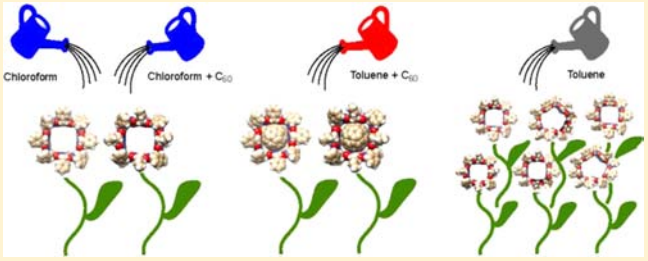
Supporting Information

ABSTRACT: Synthesis, solvent-, and guest-controlled self-assembly, and self-sorting of new hydrogen-bonded chiral cavity receptors are reported. The design of the cavity is based on the cyclic self-aggregation of monomers containing the 4H-bonding ureidopyrimidinone motif fused with the bicylo[3.3.1]nonane framework. Selective formation of kinetically inert cyclic tetramers is observed in chloroform, while in toluene an equilibrium between tetrameric and pentameric forms exists. The high affinity of the tetrameric aggregates toward C_{60} and C_{70} is observed in aromatic solvents. The host–guest interaction of unconventional π-acidic supramolecular receptors for fullerenes is turned off and on by changing the solvent, whereas the selection of size and the very composition of the cavity aggregate is controlled by either the change of solvent or the addition of fullerene guest, making our systems a new type of self-sorting device.



INTRODUCTION

The rich host–guest chemistry of covalent cyclic compounds with a well-defined three-dimensional cavity such as cyclodextrins,[1] cucurbiturils,[2] calixarenes[3] or recently introduced pillararenes[4] is at the core of supramolecular chemistry. Applications as diverse as enzyme mimicking,[5] formation of supramolecular polymers,[6] rotaxanes,[7] functional inclusion complexes[8] or asymmetric synthesis with chiral cavities[9] have been achieved indicating a tremendous potential of these structures. As opposed to molecular capsules, their open-end structural feature is also of special interest as it could potentially be exploited for rim-to-rim assembly to produce tubular polymers, decoration with additional groups of functional relevance or threading many host units by single polymeric guest.[10] Although very useful, the covalent cyclic structures are not always straightforward for synthesis by conventional methods, especially when a large or tailor-made cavity is desired. The fixed size and rigidity of the cavity are yet other important limitations of the covalent structures mentioned above. Many of these drawbacks could be overcome when the supramolecular approach, utilizing relatively small, easily available, and modifiable building blocks, is pursued to construct cyclic cavity compounds. To reliably guide the self-assembly process, the hydrogen bonds are ideal candidates due to their directionality and reversibility. The choice of the hydrogen-bonding motif becomes very important in order to provide the cavity with the desired stability, size, and function.[11] However, the majority of the known hydrogen-bonded cyclic aggregates are achiral and planar and possess no three-dimensional cavity for host–guest complex formation.[12] Herein we introduce the first functioning chiral cyclic cavity receptor self-assembled by hydrogen bonds: the monomers **1** and **2** contain the quadruple hydrogen bonding unit of ureidopyrimidinone (UPy)[13] attached to each end of an enantiopure C_2-symmetric bicyclo[3.3.1]nonane backbone (Figure 1a). In this way the hydrogen-bonding motifs in the monomer are positioned at ~90° angles. The monomers are thus predisposed to cyclic tetramer formation; however, small variations in the hydrogen bonding angle would, in principle, also allow the formation of larger aggregate, e.g., pentamer or hexamer.[14] The so obtained central cavity of the aggregates can be used to accommodate suitable guests while a straightforward synthesis of many different urea derivatives enables the introduction of a handle for structure and function modulation (Figure 1b).[15]

The dynamic nature of the cavity coupled with its host–guest chemistry provides a perfect platform to investigate self-sorting properties of monomers having different urea

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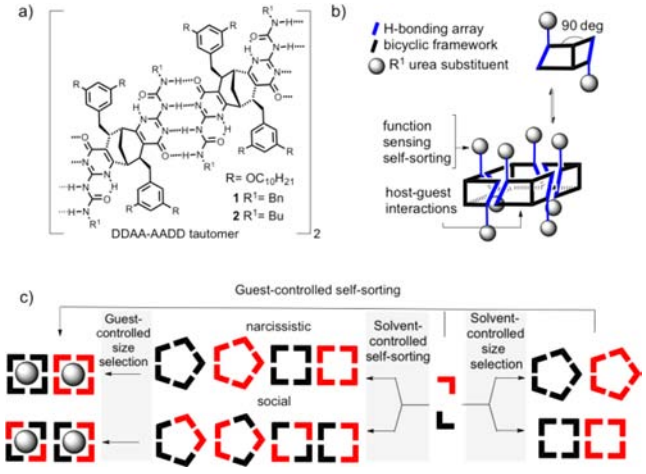


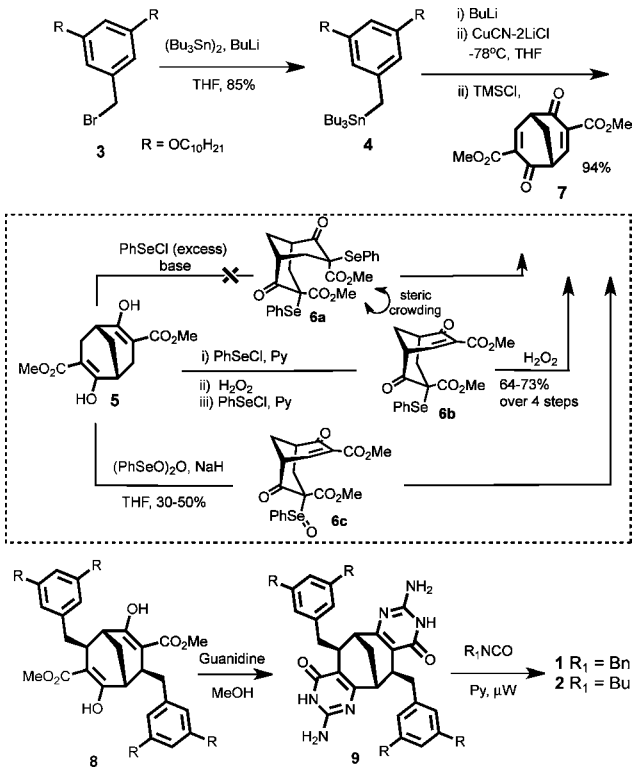
Figure 1. (a) Chemical structure of quadruply H-bonding monomers **1**, **2** used in this study in their self-assembled form. (b) Schematic representation of monomers **1**, **2** and cyclic supramolecular aggregates $\mathbf{1}_4$, $\mathbf{2}_4$. (c) Possible utilization of cavity monomers **1**(black) and **2** (red) in solvent- and guest-controlled cavity size selective self-sorting setups.

substituents and test how the cavity size and sorting fidelity could be controlled by the choice of solvent or guest (Figure 1c). In this paper, we now realize these objectives by the use of monomers **1** and **2**, the different properties of chloroform and toluene as solvents and C_{60} as guest.

RESULTS AND DISCUSSION

Synthesis. The synthesis of monomers **1** and **2** is outlined in Scheme 1. The ureidopyrimidinone ring was assembled in two steps from the corresponding ketoester **8** by first condensing it with guanidinium chloride under basic conditions and then treating the obtained isocytosine derivative **9**[14,16] with the corresponding isocyanate under microwave irradiation in pyridine. In order to secure a high solubility of the monomers in nonpolar solvents, the branched solubilizing chains of 3,5-bis(decyloxy)benzyl were attached at the 4,8-*exo,exo* positions of the bicyclic framework using organocopper chemistry. It is worth noting that the Michael acceptor **7** can only be obtained in good yield when a stepwise selenation−oxidation−elimination sequence is applied. The attempts to prepare compound **7** via direct bis selenation were unsuccessful because of the steric crowding that arises between two *endo* ester groups in the intermediate **6a** (Scheme 1) forcing one of the cyclohexane rings to adopt an energetically unfavorable boat conformation. In contrast, after elimination of the first phenyl selenoxide group from the monoselenated compound, the unsaturated cyclohexane ring is flattened to a sufficient extent to allow the second selenation to proceed without any problems (Scheme 1, intermediate **6b**). The importance of steric factors was further corroborated by the successful one-step synthesis of **7** using phenylselenic anhydride where selenium was introduced in the highest oxidation state (Scheme 1, intermediate **6c**) to ensure its immediate elimination, thus avoiding the steric repulsion observed in **6a**. A rather moderate yield of this transformation was mainly attributed to a poor quality of commercial reagent employed.[17] The synthesis of the required benzylic organometallic derivative proved to be challenging as well because the electron-rich aromatic ring caused an extensive Wurtz coupling side reaction. This problem was solved by using tin−lithium exchange with compound **4**, which in turn was synthesized in high yield from the corresponding bromide **3** and tributyltin lithium. The smooth lithiation of **4** with a subsequent transmetalation with copper and trimethylsilyl chloride mediated 1,4-addition to **7** resulted in almost quantitative yield of *β*-ketoester **8**.

Scheme 1. Synthesis of Monomers 1 and 2



Self-Aggregation Studies. The first indication of strong association of **1** came from the ^{1}H NMR spectrum of diluted **1** in $CDCl_3$ (Figure 2a), showing three well-defined downfield singlet resonances at 12.65, 11.96, and 10.14 ppm assigned to hydrogen-bonded UPy. The second indication was provided by the ^{1}H NMR dilution titration of **1** in $CDCl_3$ from 52.8 to 0.025 mM (Figure S38, Supporting Information). No shift or appearance of the new resonances was observed over these concentrations, confirming the presence of a stable aggregate. The high symmetry of the ^{1}H and ^{13}C spectra of **1** is in accordance with a well-defined cyclic aggregate since simple dimers are unlikely to form due to a geometric preorganization of the enantiomerically pure monomer. Among the three different tautomeric forms UPys displays, the 4[1*H*]-pyrimidinone and pyrimidin-4-ol tautomers can self-aggregate by the DDAA−AADD and the DADA−ADAD hydrogen-bonding motif, respectively.[13a] The ^{15}N−^{1}H HMQC spectrum of **1** in $CDCl_3$ showed that all three most downfield resonances belong to protons bound to nitrogen atoms (Figure S12, Supporting Information), demonstrating the DDAA mode of H-bonding.

The strong self-association of **1** was also confirmed by further NMR titration and VT-NMR experiments: the aggregate of **1** was stable until the addition of 20% (v/v) DMSO-d_6 in $CDCl_3$. Moreover, VT NMR of **1** in $CDCl_3$ indicated a small degree of dissociation only at 363 K (Figures S39 and S40, Supporting Information).

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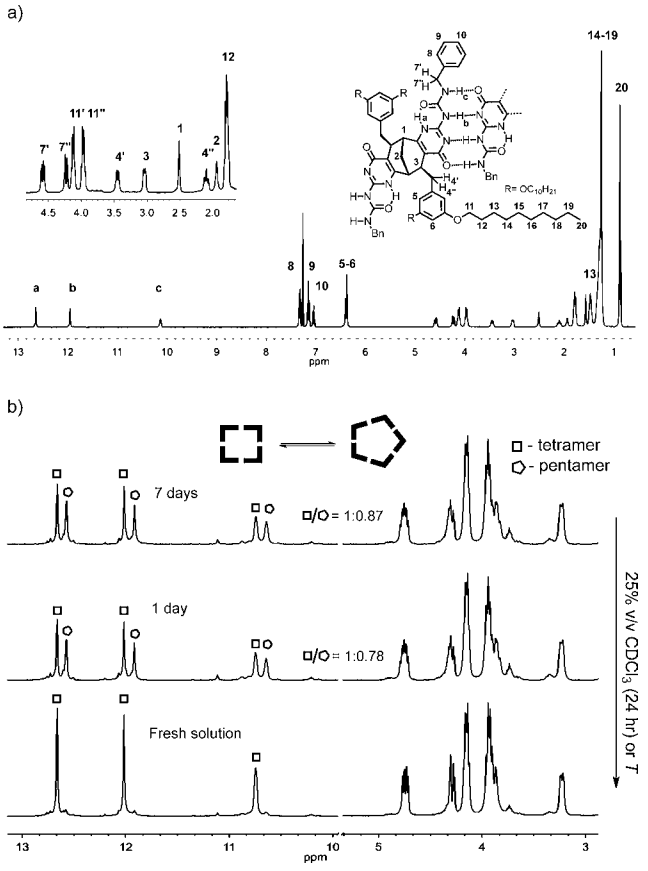

Figure 2. (a) ^{1}H NMR spectrum of **1** in $CDCl_3$ and (b) in toluene-d_8, showing an evolution of the equilibrium between tetramers and pentamers controllable by the content of $CDCl_3$ and temperature.

To obtain information about the size of the aggregate, diffusion-ordered ^{1}H NMR spectroscopy (DOSY) experiments were carried out on a 2 mM solution of **1** in $CDCl_3$ at 293 K (Figure S41, Supporting Information). The DOSY spectrum showed a correlation of all resonances to the same diffusion coefficient $D = 2.9 \cdot 10^{-10}$ m^2 s^{-1}, supporting the existence of a single aggregate. The size and diffusion coefficient of tetrameric $\mathbf{1}_4$ and pentameric $\mathbf{1}_5$ aggregates in $CDCl_3$ were calculated using all-atom molecular dynamics (MD) simulations (see the Supporting Information). The diffusion coefficients were $2.8 \cdot 10^{-10}$ and $1.9 \cdot 10^{-10}$ m^2 s^{-1} for $\mathbf{1}_4$ and $\mathbf{1}_5$, respectively. Thus, the statistical mechanical modeling is in remarkably close agreement with experimental data, suggesting that **1** exists predominantly as $\mathbf{1}_4$ in $CDCl_3$. Comparison of *D*s from experiments and MD to obtain the size of the aggregate is based on first principles and is therefore more correct than other methods.[18] This example is to our knowledge the first where such a comparison for large self-assembled aggregates has been done.

Gel permeation chromatography on **1** using $CHCl_3$ as eluent and a set of derivatized β- and γ-cyclodextrins as standards confirmed the DOSY results that the aggregate of **1** is monodisperse, PDI = 1.01 (PDI- polydispersity index, PDI = M_w/M_n) and tetrameric (M_w(exp) = 5910, M_w(theor for $\mathbf{1}_4$) = 5428, M_w(theor for $\mathbf{1}_5$) = 6785). The final compelling evidence for the formation of $\mathbf{1}_4$ was obtained from vapor pressure osmometry affording an average degree of polymerization DP = 3.86 over the wide concentration range (see the Supporting Information).

The ^{1}H NMR spectra of **1** and **2** in a variety of nonpolar solvents showed the same pattern of quadruple hydrogen bonding, which was insensitive to dilution. However, in stark contrast to the $CDCl_3$ solution, solutions of **1** and **2** in toluene-d_8 or benzene-d_6 underwent changes within a few hours with the emergence of another set of resonances (Figure 2b). It is well-known from previous studies on UPys[13a] that the content of enolic form increases significantly in the less polar toluene compared to $CHCl_3$, and it was therefore initially reasoned that the new set of resonances might belong to the cyclic tetramer involving the pyrimidin-4-ol tautomer of **1**. Surprisingly, ^{15}N−^{1}H HMQC revealed the presence of 4[1*H*]-pyrimidinone as the only tautomer of **1** in toluene-d_8. This strongly suggested that the new species was a supramolecular homologue of $\mathbf{1}_4$. Indeed, DOSY experiments in toluene-d_8 (Figure S42, Supporting Information) clearly showed the coexistence of two aggregates, and the ratio of the diffusion coefficients was found to be 1.08. This was in agreement with a predicted value using a known relationship between the molecular weight of the aggregate and the diffusion coefficient, assuming averaged spherical aggregates of a tetramer and a pentamer (see the Supporting Information).[19] The molar ratio of the two aggregates was found to be concentration dependent; a higher content of the larger aggregate was observed for more concentrated solution, suggesting the existence of an equilibrium between the aggregates. Fitting the theoretical models for hypothetical trimer−tetramer, tetramer−pentamer, tetramer−hexamer, and pentamer−hexamer equilibria to the experimentally obtained size-corrected equilibrium molar ratios of two species at different concentrations of **1** and **2** gave the best fit to the tetramer−pentamer model, with the macroscopic constants $K = 90.8 \pm 4.7$ M^{-1} and 35.0 ± 3.7 M^{-1} for **1** and **2**, respectively, in toluene-d_8. The thermodynamic values $\Delta H^\circ = -81.1 \pm 4.0$ kJ mol^{-1} and $\Delta S^\circ = -254.1 \pm 13.1$ J mol^{-1} K^{-1} in toluene-d_8 were estimated from a van't Hoff plot for the tetramer−pentamer equilibrium of **1** (Figure S48, Supporting Information). As seen, the process is highly exothermic; however, the large entropic penalty for the reassembly of large number of monomers results in a rather modest ΔG°. The higher stability of cyclic pentamers in toluene is probably related with specific solvent effects, including solvation and encapsulation processes, since DFT calculations in the gas phase give very similar estimates of binding energies for tetramers $\mathbf{1}_4$, $\mathbf{2}_4$ and pentamers $\mathbf{1}_5$, $\mathbf{2}_5$ (Table S3, Supporting Information). Moreover, no pentamers were detected in $CDCl_3$ suggesting that the cavity of the tetramer is highly stabilized by inclusion of a few $CDCl_3$ molecules, while the stronger hydrogen bonding in less polar toluene can tolerate larger distortions of the hydrogen bonding angle, thus making larger aggregates possible. The effect of $CDCl_3$ is pronounced, and addition of only 25% of $CDCl_3$ into toluene-d_8 resulted in complete conversion of $\mathbf{1}_5$ to $\mathbf{1}_4$ (Figure 2b). Combined, these observations show unique examples of solvent-responsive selection of sizes of supramolecular aggregates.

The molecular modeling of the geometry of $\mathbf{1}_4$ and $\mathbf{2}_4$ suggested that each cavity is 13.0 Å from face to face and thus could fit one molecule of C_{60} or C_{70}.[20] An almost perfect match is observed on the basis of the van der Waals radii of C_{60} and the cavity (Figure 3a). DFT calculations in the gas phase indicated that the complex $\mathbf{C_{60}@1_4}$ is more stable than $\mathbf{1}_4$ by 45 kJ mol^{-1} (see the Supporting Information). Upon addition of C_{60} to a fresh solution of **1** in toluene-d_8, the immediate formation of an inclusion complex was evidenced by the

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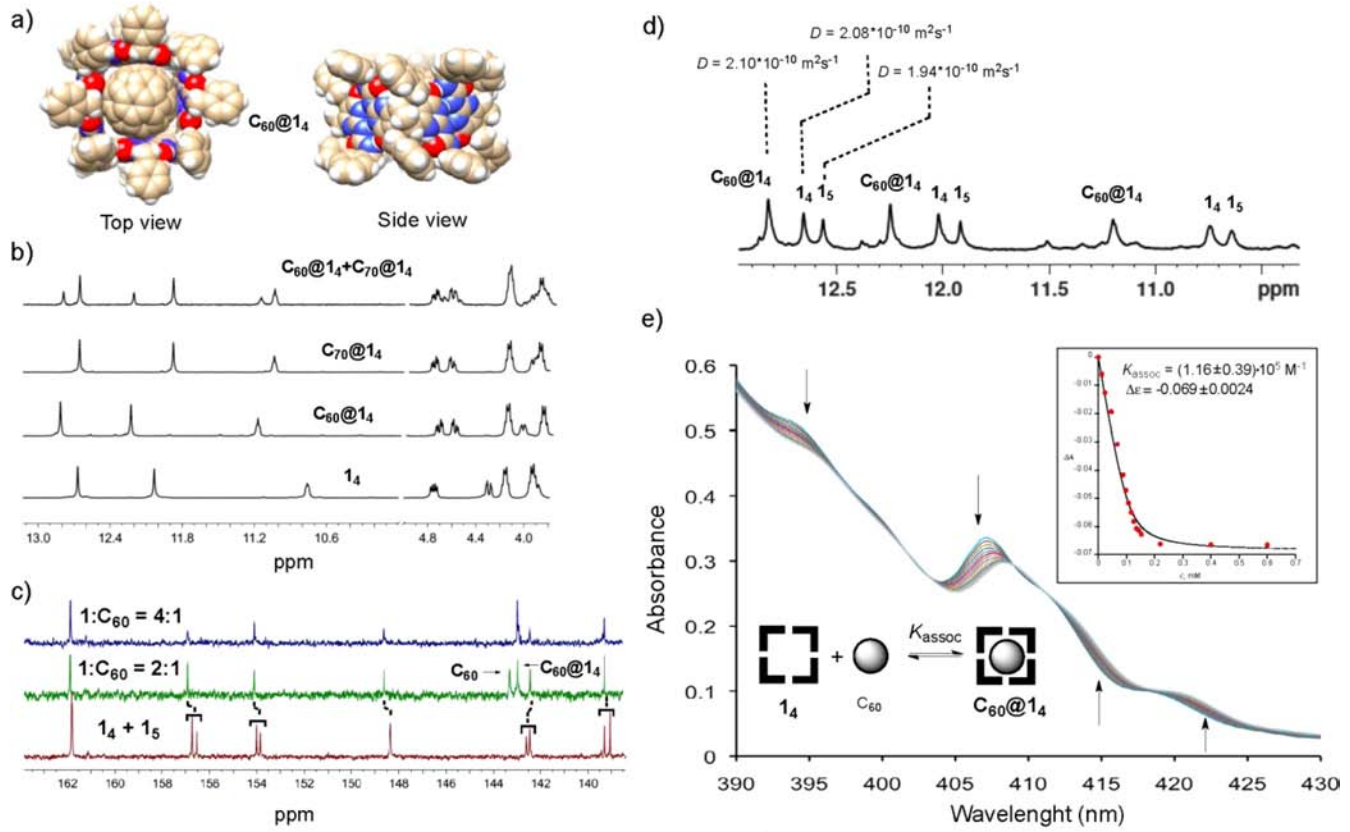

Figure 3. (a) Model of C_{60}@1_4. Alkyl chains were omitted for clarity. (b) Part of ^{1}H NMR spectra of 1_4 (bottom), C_{60}@1_4 and C_{70}@1_4 (middle), and mixture of 1_4, C_{60}, and C_{70} (top) in toluene-d_8. (c) Part of ^{13}C NMR spectra of aged solution of 1 in toluene-d_8 with different amounts of C_{60} guest. The formation of a single inclusion complex was evident from the emergence of a new set of resonances upon addition of C_{60}. (d) ^{1}H NMR spectrum of a mixture composed of 1_4, 1_5, and C_{60}@1_4 in toluene-d_8, obtained from aged solution of **1** and deficient amount of C_{60}. The values of measured diffusion coefficients of each species are given above the spectrum. (e) Spectrophotometric titration of C_{60} with a fresh solution of 1_4 in toluene. The arrows indicate the corresponding change of C_{60} absorption upon increasing concentration of 1_4. The inset displays the fitting of a 1:1 binding isotherm to the titration data.

downfield shift of resonances of the NH and benzylic protons belonging to the urea side-chains (Figure 3b, bottom and middle). The ^{13}C NMR spectra showed an upfield shift of the C_{60} resonances by 0.4 ppm as a result of the shielding effect of the isocytosine walls. Accordingly, the ^{13}C signals of the isocytosine moiety were shifted downfield (Figure 3c). The binding stoichiometry of 1:1 between 1_4 and C_{60} was confirmed by the molar ratio method using ^{1}H NMR titration. The binding constant $K = (1.16 \pm 0.39)\cdot10^5$ M^{-1} for C_{60}@1_4 was determined from UV titrations in toluene (Figure 3e). The absorption spectrum of the C_{60} guest was followed during the titrations, and the most notable change occurred at 407 nm where a decrease of the absorption and a small bathochromic shift (ca. 2 nm) was observed upon increasing the concentration of receptor 1_4.[21] The presence of several isosbestic points in the UV spectra is suggestive of a simple equilibrium between two species. The magnitude of K is quite impressive taking into account the electron-deficient nature of the isocytosine ring and represents a rare example of a complex between a fullerene and a π-acidic host.[22] The selectivity of 1_4 toward C_{60} and C_{70} was accessed from ^{1}H NMR measurements in toluene-d_8 using a 1:1 mixture of C_{60} and C_{70} in excess and was found to be 1:2 (C_{60}:C_{70}) (Figure 3b, top). The higher stability of C_{70}@1_4 can be explained by the larger π-surface of C_{70} available for interaction with the isocytosine units. Interestingly, when the complexation was performed with the aged solution of **1** consisting of a mixture of 1_4 and 1_5 and excess C_{60}, the selective formation of complex C_{60}@1_4 was observed with the accompanying disappearance of 1_5 as indicated by ^{1}H, ^{13}C, and DOSY NMR spectra (Figure 3c). The identity of C_{60}@1_4 was unambiguously proven by DOSY measurement of a mixture composed of an excess of **1** and C_{60}. Under these conditions, all C_{60} is consumed for C_{60}@1_4, whereas remaining **1** equilibrates between tetrameric 1_4 and pentameric 1_5 forms. All three aggregates can be observed simultaneously in the ^{1}H NMR spectrum, and DOSY experiments revealed that C_{60}@1_4 and 1_4 have the same diffusion coefficient (Figure 3d). DFT calculations also supported the experimentally observed selectivity and indicated a higher stability of C_{60}@1_4 due to a better match between the size of its cavity and C_{60} as compared to C_{60}@1_5 (see the Supporting Information). Remarkably, no complex formation was observed in $CDCl_3$ solution between either 1_4 or 2_4 and C_{60}, even after prolonged heating followed by cooling to rt. This observation is opposite the well-known inverse correlation between fullerene solubility and complex stability.[23] It suggests that desolvation of the receptor cavity and not of C_{60} is the dominant factor in the thermodynamics of complex formation. An attempt to prepare the C_{60}@1_4 complex in $CDCl_3$ by solvent exchange from toluene to $CDCl_3$ was unsuccessful and resulted in C_{60} precipitation, indicating preferential filling of the cavity of 1_4 with $CDCl_3$, rather than C_{60} molecules.

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Self-Sorting. In the context of functional supramolecular systems, the simultaneous existence of multiple aggregates is often required for specific function, morphology, or stimuli response. The concept of self-sorting has been introduced to describe self- or nonself-recognition of different monomers in their mixture[24] and has since then been widely applied.[25] We wanted to test the possible self-sorting ability of **1** and **2** in different solvents imposed by their different urea substituents and also to see if the self-sorting could be tuned by C_{60} insertion. First, compounds **1** and **2** were mixed in toluene-d_8 in a 1:1 molar ratio (Figure 4, process A), resulting in no

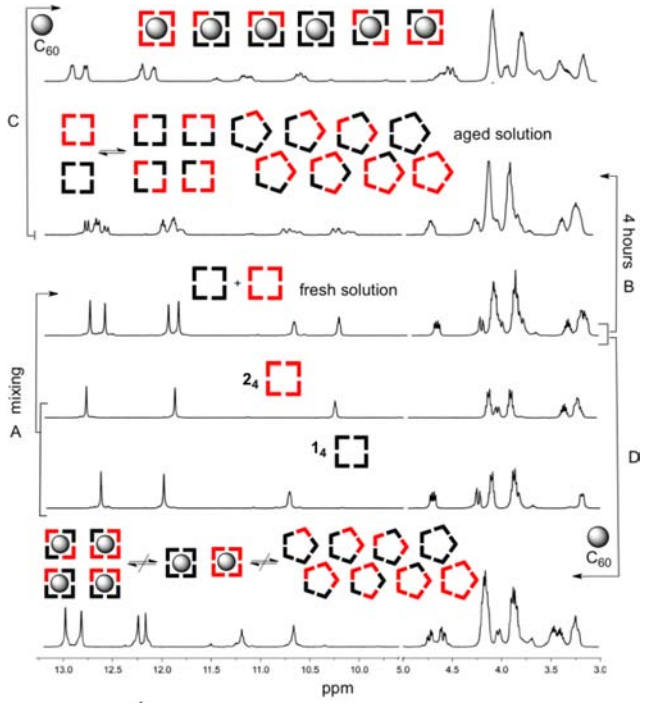

Figure 4. ^{1}H NMR spectra and schematic representation of self-sorting of $\mathbf{1}_4$ and $\mathbf{2}_4$ in toluene-d_8 solution as a function of time and added C_{60} guest.

scrambling; however, after a short period an exchange of monomers started. The process was completed in 4 h, and a mixture of scrambled tetramers and pentamers was obtained (Figure 4, process B). This finding was consistent with very similar energies of $\mathbf{1}_4$ and $\mathbf{2}_4$ obtained from DFT calculations (see the Supporting Information). Addition of C_{60} to the above mixture removed all pentamers from the equilibrium leaving only the mixture of tetrameric insertion complexes (Figure 4, process C). In contrast, addition of C_{60} to the fresh mixture of **1** and **2** led to the "freezing" of $\mathbf{1}_4$ and $\mathbf{2}_4$ and formation of homoleptic $\mathbf{C_{60}@1_4}$ and $\mathbf{C_{60}@2_4}$ with negligible mixing of monomers as compared to the C_{60}-free solution (Figure 4, process D). The insertion of C_{60} thus increased the kinetic barrier required for monomer interchange and resulted in kinetic self-sorting of $\mathbf{1}_4$ and $\mathbf{2}_4$. The monomer exchange between complexes $\mathbf{C_{60}@1_4}$ and $\mathbf{C_{60}@2_4}$ was not observed even at 353 K as demonstrated by VT NMR experiments (Figure S64, Supporting Information). When **1** and **2** were dissolved in $CDCl_3$, no detectable mixing was observed over time, showing a very efficient kinetic self-sorting in this solvent. The self-sorting properties of compounds **1** and **2** in $CDCl_3$ are impressive considering the subtle differences in their structure.

CONCLUSIONS

We have reported the first example of enantiomerically pure supramolecular cavity aggregates assembled by a quadruple H-bonding motif. Each aggregate possesses a cavity composed of DDAA−UPy fused bicyclic monomers **1** and **2**. The monomers undergo a unique solvent-responsive selective self-assembly to cyclic $\mathbf{1}_4$ and $\mathbf{2}_4$ in $CHCl_3$ and to a mixture of cyclic $\mathbf{1}_4$, $\mathbf{2}_4$, and cyclic $\mathbf{1}_5$, $\mathbf{2}_5$ in toluene. In addition, when mixed together these monomers display self-sorting properties, which are responsive to the choice of solvent or to C_{60}. Hence, the exclusive formation of kinetically inert homoleptic assemblies $\mathbf{1}_4$ and $\mathbf{2}_4$ was observed in $CHCl_3$, whereas in toluene a mixture of scrambled tetramers and pentamers was obtained. The tetramers $\mathbf{1}_4$ and $\mathbf{2}_4$ constitute a new class of efficient fullerene receptors based on unconventional π-acidic structural units that complex C_{60} and C_{70} in aromatic solvents. The kinetic properties of the two structurally very similar receptors $\mathbf{1}_4$ and $\mathbf{2}_4$ were switched from highly labile to inert by C_{60} inclusion. The incremental tuning of the cavity size as well as the composition of the cavity by solvent can find applications in catalysis and recognition where a subtle match between the size of the transition state of substrate or guest and that of the receptor must exist for best performance. The open-end feature of the described tetramers can be potentially exploited to achieve diameter selective solubilization of carbon nanotubes. We are now functionalizing the end-group on the urea moiety of the cavity with the aim of making a self-assembled rim-to-rim nanotube.

ASSOCIATED CONTENT

Supporting Information

Synthesis and characterization of monomers **1** and **2** and their aggregates in different solvents; experimental and computational details for diffusion coefficients, inclusion complexes, and tetramer−pentamer equilibrium. 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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