

An Enantiopure Hydrogen-Bonded Octameric Tube: Self-Sorting and Guest-Induced Rearrangement

Dovilė Račkauskaitė, Rokas Gegevičius, Yutaka Matsuo, Kenneth Wärnmark,* and Edvinas Orentas*

Abstract: The assembly of a discrete hydrogen-bonded molecular tube from eight small identical monomers is reported. Tube assembly was accomplished by means of selective heterodimerization between isocytosine and ureidopyrimidinone hydrogen-bonding motifs embedded in an enantiopure bicyclic building block, leading to the selective formation of an octameric supramolecular tube. Upon introduction of a fullerene guest molecule, the octameric tube rearranges into a tetrameric inclusion complex and the hydrogen-bonding mode is switched. The dynamic behavior of the system is further explored in solvent- and guest-responsive self-sorting experiments.

The rational design of noncovalent organic tubular objects having large cavities from small acyclic units is highly desired but as yet has not been achieved. Nanoscale tubular assemblies may find application in the fields of catalysis, separation, molecular encapsulation, or drug delivery.^[1] The investigation of the properties of molecules confined inside the cavities of both covalent and noncovalent molecular containers has become an important topic in supramolecular chemistry.^[2] The encapsulation of molecular targets within nanosized cavities has, for the first time, allowed researchers to observe phenomena that are otherwise not evident or are nonexistent in the solution phase, such as selection of a particular conformer of the flexible guest,^[3] stabilization of a reactive species^[4] or an elusive supramolecular aggregate,^[5] and changing the outcome of a chemical reaction involving the guest molecule.^[6]

To construct molecular tubular objects using hydrogen bonding (H-bonding), the general strategy is to use preorganized cyclic monomeric units equipped with a robust H-bonding motif that already encodes a large part of the information required for the shape and size of the desired aggregate. Prominent examples include molecular tubes self-

assembled from designed cyclic peptides,^[7] resorcinarenes,^[8] or oligo(*para*-phenylenes).^[9] In contrast, multicomponent assemblies from smaller monomers are still rare, most likely because of the difficulties to predict and control the outcome of the aggregation of such systems.^[10]

Over the last years, we have reported our first steps towards the highly reliable assembly of tubular aggregates using very compact H-bonding C₂-symmetric monomers based on the bicyclo[3.3.1]nonane (BCN) backbone.^[11] Using this strategy, the 3H- and 4H-bonding motifs were successfully utilized to construct self-assembled cyclic tetrameric aggregates with interesting host-guest properties.^[11b,c] Herein we demonstrate how a rationally designed nonsymmetric monomer based on the BCN backbone and having both one 3H- and one 4H-bonding motif can be assembled into an octameric tube. The assembly occurs by means of heteroaggregation between two different interacting units. Furthermore, we show that the so-obtained tubular aggregate undergoes a drastic structural octamer-tetramer rearrangement when a suitable guest is introduced into the system.

In general, when two different H-bonding monomers are combined, selective formation of homoaggregates is detected, as demonstrated in a seminal study by Isaacs and Wu.^[12] Such high association fidelity could be explained by the perfect match between the complementary H-bonding motifs and their geometric preorganization within the interacting monomers, leading to defect-free homoaggregates. However, a more complicated situation could arise in systems where one of the components is unable to form a stable homoaggregate. If two H-bonding arrays can partially overlap, a heteroaggregate could form to maximize the overall number of hydrogen bonds, thereby minimizing the free energy of the system. The concept can be demonstrated with a 1:1 mixture consisting of a 4H-bonding ureidopyrimidinone (UPy)^[13] unit and a 2H- or 3H-bonding isocytosine (ICyt) unit, as shown in Figure 1 a. In the case of homodimerization, the maximum number of H-bonds per molecule (herein defined as the H-bond index) is expected to be 3.5 at best, when two ICyt molecules are linked by three H-bonds. On the other hand, if ICyt units only weakly interact, the actual number of H-bonds is lower. The system is therefore forced towards formation of heterodimers where all the components are hydrogen-bonded.^[14] Furthermore, in this particular case the H-bond index could reach even higher values if the so-formed heterodimers aggregate further to form a tetramer using the additional H-bonding sites available. One H-bond lost from the [UPy]₂ dimer is thus fully compensated by the two newly established H-bonds in the [[Upy-ICyt]₂]₂ tetramer (Figure 1 a, right).

[*] D. Račkauskaitė, R. Gegevičius, Prof. E. Orentas
Department of Organic Chemistry, Vilnius University
Naugarduko 24, 03225 Vilnius (Lithuania)
E-mail: edvinas.orientas@chf.vu.lt

Prof. Y. Matsuo
Department of Chemistry
School of Science, The University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)

Prof. K. Wärnmark
Center for Analysis and Synthesis
Department of Chemistry, Lund University
P.O. Box 124, 22100 Lund (Sweden)

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201508362>.

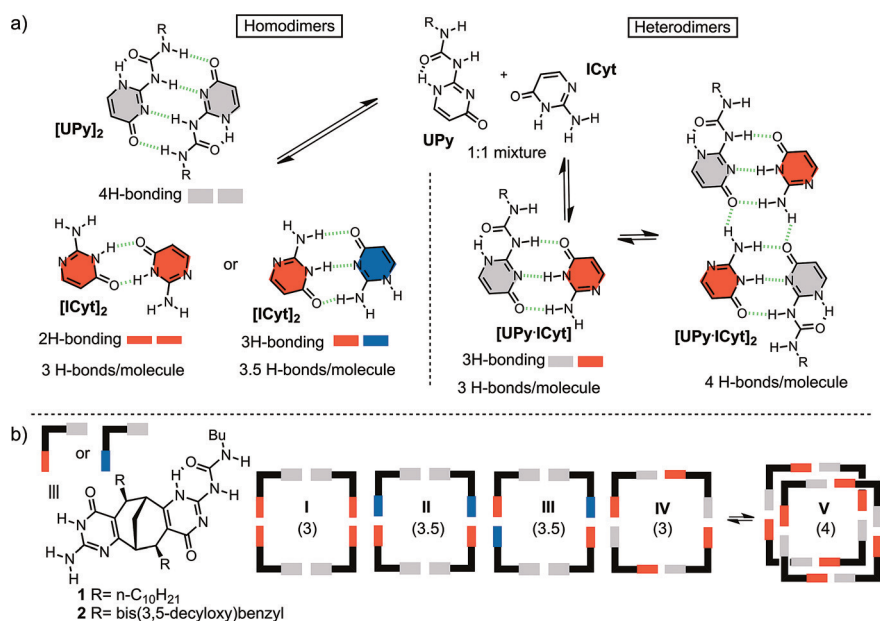


Figure 1. a) Possible self-sorting scenarios for a 1:1 mixture of isocytosine (ICyt) and ureido-pyrimidinone (UPy). b) Enantiopure bicyclic H-bonding monomers **1** and **2** and a schematic representation of possible H-bonded cyclic structures formed from assembly of the monomers. Numbers in parenthesis indicate the H-bond index (numbers of H-bonds per molecule).

To apply this idea in practice, we synthesized the enantiomerically pure bicyclic monomers **1** and **2** (see the Supporting Information), each having one Upy and one ICyt moiety fused to their respective BCN backbone (Figure 1b). We have previously shown that C₂-symmetric monomers of this type form very stable tetrameric cyclic aggregates by cooperative H-bonding.^[11b-d] According to the above-discussed aggregation scenarios, three cyclic tetramers **I–III** involving [UPy]₂ and [ICyt]₂ homoaggregation modes are possible with maximum H-bond indices of 3.5. However, we reasoned that the UPy–ICyt heteroaggregation mode should be favored in this system, resulting in a H-bond index of 4 after dimerization of two tetramers **IV** into the octameric tube **V** (Figure 1b). This strategy would enable the construction of a molecular tube with a large cavity from eight small identical building blocks.

Gratifyingly, the ¹H NMR spectra of **1** in a variety of nonpolar solvents confirmed that the [UPy-ICyt]₂ aggregation mode was indeed operating (Figure 2a). Two downfield singlets were detected at $\delta = 8.7$ ppm and 8.3 ppm in CDCl₃ attributable to the amino group protons of the ICyt moiety, corresponding to H-bonded protons. One proton is involved in the formation of the cyclic tetrameric belt and the other in the edge-to-edge connection of two such cyclic aggregates. Additionally, the NH signal for the urea moiety in the Upy fragment, connected to the butyl substituent, appeared as an upfield triplet at $\delta = 5.6$ ppm, unambiguously indicating that this proton does not participate in hydrogen bonding. Thus, the normally preferable quadruple H-bond between two Upy molecules is not formed. The diffusion-ordered (DOSY) NMR spectrum of **1** showed positive correlation of all of the resonance signals to the same diffusion coefficient, in accordance with the formation of a single aggregate. The so-

formed octamer **1₈** was stable up to 80 °C, as indicated by variable-temperature NMR spectroscopy (see the Supporting Information). Interestingly, when the solubilizing decyl side-chains on the bicyclic backbone were replaced by bulky 3,5-bis-(decyloxy)benzyl groups in **2**, no octamer was formed. Instead, a complicated mixture of aggregates was detected (see the bottom NMR spectrum in Figure 2a, showing the spectrum of aggregates of **2** in CDCl₃). Formation of this complicated mixture is as a result of the introduction of steric repulsion between the bulky side-chains of two monomers of **2** if they are connected edge-to-edge in the hypothetical octamer **2₈**. This result also stresses the importance of bifurcated H-bonds between tetrameric units for exclusive UPy–ICyt dimerization to take place. Only when these H-bonds can form (as in **1**), the selective formation of tetramers **IV** followed by octamer **V** is detected (Figure 1b). In contrast,

when this aggregation pathway is blocked, as in the case of monomer **2**, a mixture of aggregates, most likely consisting of tetramers **I–IV**, is obtained. Racemic **1** displayed the same aggregation profile as enantiomerically pure **1**, indicating its high preference for the formation of a homochiral aggregate, in contrast to structurally similar monomers, previously reported by us (see Figure S6 in the Supporting Information).^[11a,c]

Next, we explored the host–guest chemistry of the so-obtained octameric tube with fullerene guest molecules. According to molecular modelling (PM3 within Spartan¹⁰), the diameter of the cavity is well-suited for the encapsulation of C₆₀ or C₇₀ molecules (Figure 2a). Moreover, the length and the open-top topology of the host could easily allow for the accommodation of two C₆₀ molecules or one covalent dimer C₁₂₀. When solid C₆₀ was incrementally added to a [d₈]toluene solution of **1₈**, the formation of an inclusion complex was detected by means of ¹H NMR spectroscopy. At a low ratio of C₆₀ to **1** (1:C₆₀ 1:0.06), a transient species, having the same spectral pattern as the original octamer **1₈** (but at slightly different chemical shifts) was detected (Figure 2b). When a 1:C₆₀ ratio of 1:0.25 was reached, resonance signals attributable to a single complex were obtained and no changes in the ¹H NMR spectrum were detected with further addition of C₆₀. The formation of an inclusion complex was indicated by a significant simplification of the NMR spectrum and also by a remarkable shift of the triplet signal for the NH moiety of the butyl urea group from $\delta = 5.6$ ppm to 11.0 ppm. This change clearly indicates the transformation of the octamer **1₈** (with H-bonding mode Upy–ICyt) into the new tetrameric inclusion complex C₆₀@**1₄** with a H-bonding mode of [UPy-UPy]₂[ICyt-ICyt]₂ (Figure 2b). The appearance of a broad singlet arising from the free NH₂ group of the

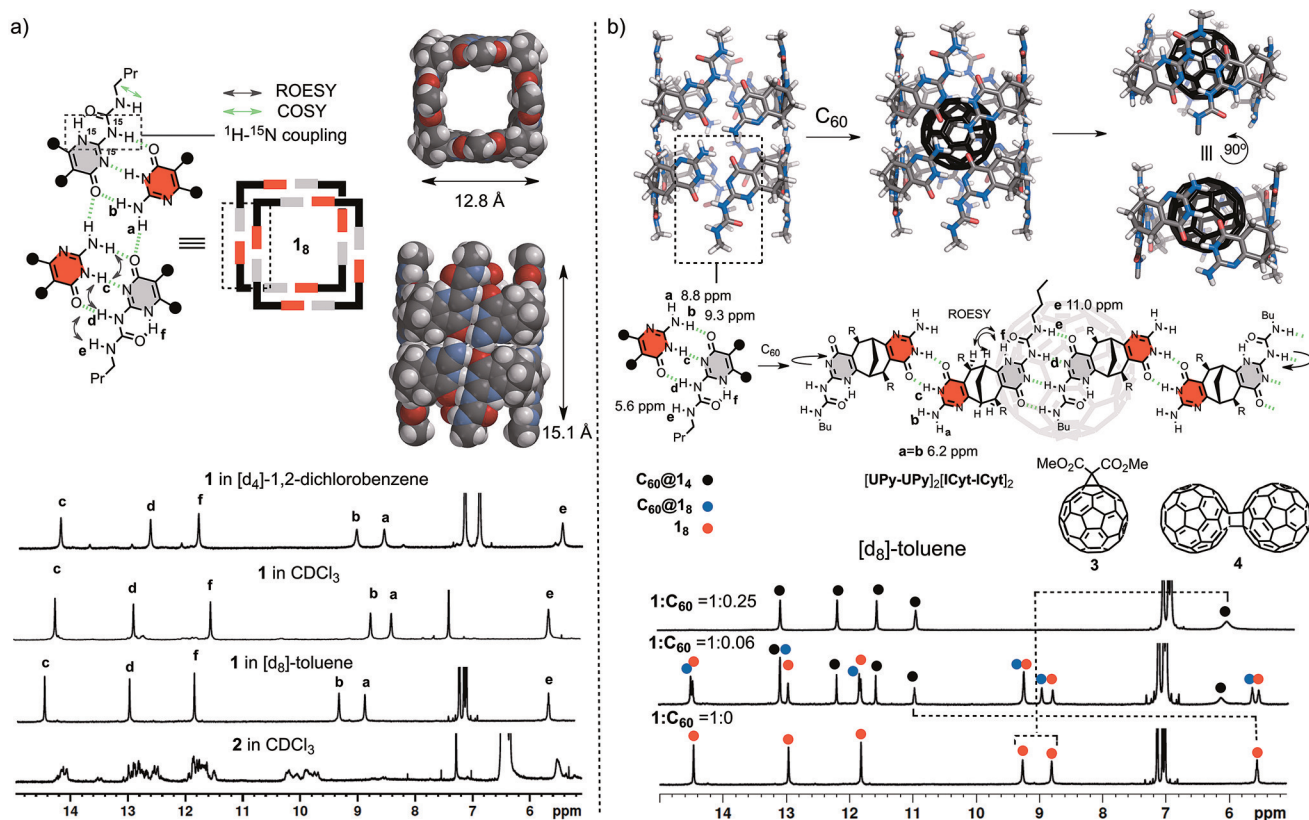


Figure 2. a) Schematic representation and molecular modelling of **1**₈ (top) and NMR characterization of **1** and **2** (bottom). b) Molecular modelling (and chemical structures showing the corresponding H-bonding interactions) showing the structural rearrangement of **1**₈ upon complexation with C₆₀ (top) and NMR titration of **1**₈ with C₆₀ in [d₈]toluene (bottom). In molecular models, the butyl chain is exchanged with a methyl group for clarity.

isocytosine fragment at $\delta = 6.2$ ppm confirms that ICyt moieties are connected together by a two hydrogen-bond interaction. On the basis of the 90° “hinge-angle” of the BCN framework of monomer **1** as well as the requirement for an even number of monomers to obtain a cyclic array, it is clear that the tetrameric assembly is the only possible assembled structure for this particular aggregation mode.^[15] The DOSY spectrum of a fresh mixture of **1** and C₆₀ consisting of three different types of aggregates revealed that the C₆₀@**1**₄ has indeed a higher diffusion coefficient than that of **1**₈. The intermediate complex has the same diffusion coefficient as **1**₈ and therefore it corresponds to the octameric complex C₆₀@**1**₈ with a symmetrically located C₆₀ molecule in the middle of the tube (see the Supporting Information). The metastable C₆₀@**1**₈ is gradually converted over time into the thermodynamically more stable C₆₀@**1**₄, as indicated by ^1H NMR experiments. The integration of the ^1H NMR spectrum with only C₆₀@**1**₈ and C₆₀@**1**₄ present confirmed the stoichiometry of aggregate **1**₈ (see the Supporting Information). The same complexation events were also observed in CDCl₃ solution or using C₇₀ as the guest (Figure S24). Interestingly, functionalized C₆₀ derivatives, such as bis(methoxycarbonyl)methano-C₆₀ (**3**) and the covalent C₆₀-dimer C₁₂₀ (**4**), produced very little or none of the corresponding inclusion complexes, respectively (Figure S27; see Figure 2b for structures of **3** and **4**).

For the possible application of this guest-induced octamer–tetramer switch in systems chemistry,^[16] we decided to employ this equilibrium in more complex self-sorting^[17] setups with another competing monomer. The 4H-bonding C₂-symmetric monomer **5** (Figure 3a),^[11b] having the same shape as **1** but more bulky solubilizing chains, was chosen as a model compound to test if the cyclic octamer **1**₈ could be formed. When compounds **1** and **5** were mixed in CDCl₃ in a 1:1 ratio, a complicated mixture was obtained soon after (Figure 3b,c; process A). This mixture, resulting from non-integrative self-sorting,^[18] consists mainly of mixed tetrameric aggregates formed by 3H- and 4H-bonding with almost no octamer **1**₈ remaining, as revealed by ^1H NMR spectroscopy.^[19] The addition of an excess of C₆₀ to the mixture resulted in the selective formation of the C₆₀@**1**₄ complex and free **5**₄ as the major species together with a small amount of monomers distributed in mixed aggregates **1**_n**5**_m (Figure 3b,c; process B). From our previous studies,^[11b] it is known that C₆₀ fullerene cannot be included within tetramer **5**₄ in chlorinated solvents. Therefore, the incomplete self-sorting of the mixture is mainly driven by selective complexation of C₆₀ by a single component, namely monomer **1**. The fact that no changes in chemical shift were detected for the large part of the remaining resonance signals suggested that the mixed aggregates **1**_n**5**_m are very poor hosts for C₆₀. On the other hand, if C₆₀ was added to a fresh solution of **1** and **5** in [d₈]toluene, the

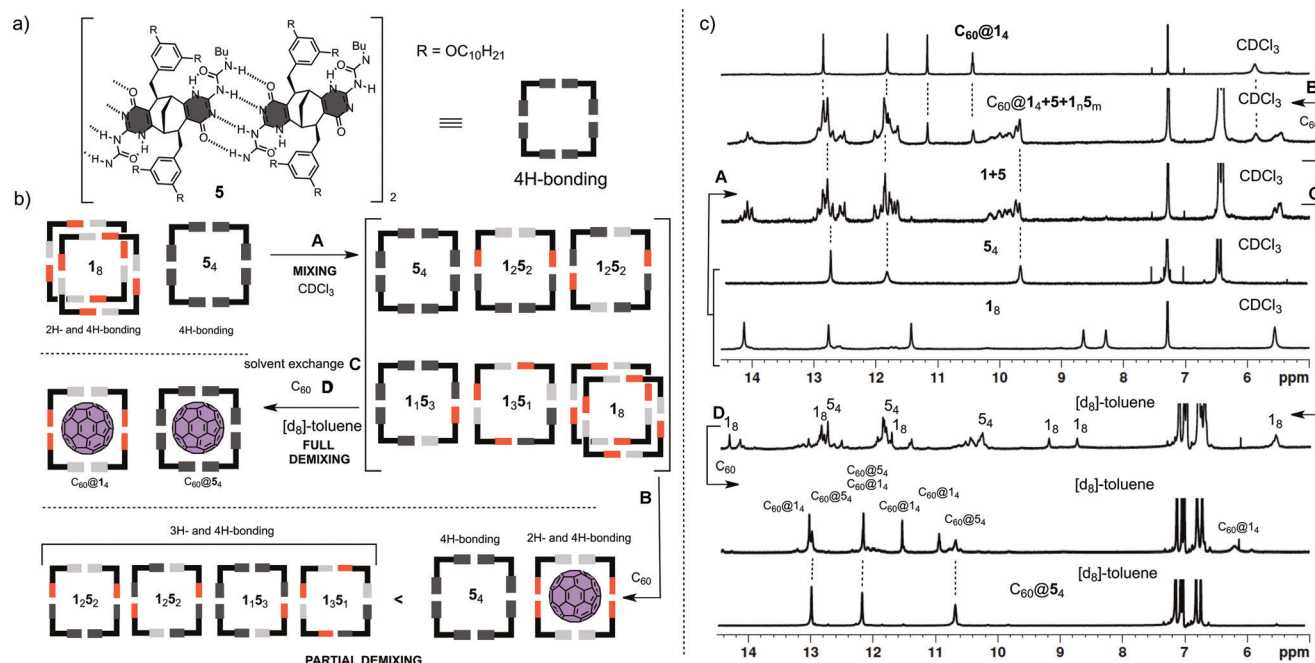


Figure 3. a) Chemical structure of the 4H-bonding monomer **5**. b) Schematic representation of the self-sorting experiment. Process A: mixing of monomers **1** and **5** in CDCl_3 resulting in a mixture of cyclic aggregates. Process B: partial separation of the mixture upon selective C_{60} complexation by monomer **1**. Process C: solvent exchange from CDCl_3 to $[\text{d}_8]\text{-toluene}$. Process D: full demixing of monomers upon treatment with C_{60} . c) ^1H NMR spectra corresponding to processes A–D.

kinetically stable homocomplexes $\text{C}_{60}@\mathbf{1}_4$ and $\text{C}_{60}@\mathbf{5}_4$ were obtained. These showed no monomer scrambling over an extended period of time (Figure S36). Interestingly, in contrast to the situation in the CDCl_3 solution, the mixture of **1** and **5** in $[\text{d}_8]\text{-toluene}$ without C_{60} do not exchange monomers to any substantial degree (Figure S37). The solvent exchange from CDCl_3 to $[\text{d}_8]\text{-toluene}$ of the fully scrambled mixture of monomers **1** and **5** afforded a mixture displaying resonance signals for systems **1**₈ and **5**₄, thus indicating partial enrichment of these homoaggregates (Figure 3c; process C). Remarkably, when C_{60} (0.25 equiv for each monomer) was added to the above mixture, complete self-sorting into the homoleptic inclusion complexes $\text{C}_{60}@\mathbf{1}_4$ and $\text{C}_{60}@\mathbf{5}_4$ was detected after several hours (Figure 3c; process D). These results indicate that for the efficient demixing of the monomers in the cyclic aggregates, the formation of two very stable homoleptic inclusion complexes is necessary. The higher stability of these complexes compared to their scrambled analogues is most likely related to their higher symmetry, providing an optimum cavity size and arrangement of the π surface for a C_{60} template. The propensity of the system for the formation of complexes $\text{C}_{60}@\mathbf{1}_4$ and $\text{C}_{60}@\mathbf{5}_4$ is also noteworthy as it works against the natural tendency of the system to release the steric pressure imparted by bulky side-chains in **5**₄ to a more relaxed state in the mixed aggregates **1**_n**5**_m.

In conclusion, we have, for the first time, assembled a hydrogen-bonded molecular tube by developing a new strategy to obtain tubular H-bonded aggregates using eight small identical monomers. The formation of a heterodimer by means of three hydrogen bonds between the ureidopyrimidinone and isocytosine motifs gives rise to a new H-bonding interface connecting two tetrameric cyclic units into an open-end supramolecular tube. In our approach, this unique type of aggregation is driven by the increase of the total number of hydrogen bonds in the system, resulting in the disruption of the otherwise extremely stable quadruple H-bonds between the ureidopyrimidinone motifs. We also show that it is possible to resolve a complex dynamic library of scrambled aggregates into homoleptic inclusion complexes by the synergetic action of toluene and a C_{60} guest. Further exploration of the host–guest chemistry of the octameric receptor with guests of practical importance is underway in our laboratories.

none and isocytosine motifs gives rise to a new H-bonding interface connecting two tetrameric cyclic units into an open-end supramolecular tube. In our approach, this unique type of aggregation is driven by the increase of the total number of hydrogen bonds in the system, resulting in the disruption of the otherwise extremely stable quadruple H-bonds between the ureidopyrimidinone motifs. We also show that it is possible to resolve a complex dynamic library of scrambled aggregates into homoleptic inclusion complexes by the synergetic action of toluene and a C_{60} guest. Further exploration of the host–guest chemistry of the octameric receptor with guests of practical importance is underway in our laboratories.

Acknowledgements

The research was funded by the European Social Fund under a Global Grant Measure (VP1-3.1-ŠMM-07-K-03-007). D.R. acknowledges support from the Research Council of Lithuania through the project “Promotion of Student Scientific Activities” (VP1-3.1-ŠMM-01-V-02-003). The Swedish Research Council is also acknowledged for funding. We are grateful to Lukas Taujienis (Department of Analytical and Environmental Chemistry, Vilnius University) for assistance with mass spectrometry and Prof. Lars Ivar Elding (Lund University) for valuable comments.

Keywords: fullerenes · hydrogen bonds · inclusion compounds · self-sorting · supramolecular chemistry

How to cite: *Angew. Chem. Int. Ed.* **2016**, 55, 208–212
Angew. Chem. **2016**, 128, 216–220

- [1] a) M. A. Balbo Block, C. Kaiser, A. Khan, S. Hecht, *Top. Curr. Chem.* **2005**, 245, 89; b) *Molecular- and Nano-Tubes* (Eds.: O. Hayden, K. Nielsch), Springer, Berlin, **2011**.
- [2] For selected reviews, see: a) D. J. Cram, J. M. Cram, *Container Molecules and Their Guests*, Royal Society of Chemistry, Cambridge, **1997**; b) M. M. Conn, J. Rebek Jr., *Chem. Rev.* **1997**, 97, 1647; c) J. Rebek Jr., *Angew. Chem. Int. Ed.* **2005**, 44, 2068; *Angew. Chem.* **2005**, 117, 2104; d) S. M. Biroš, J. Rebek Jr., *Chem. Soc. Rev.* **2007**, 36, 93.
- [3] D. Ajami, J. Rebek Jr., *Nat. Chem.* **2009**, 1, 87.
- [4] a) D. J. Cram, M. E. Tanner, R. Thomas, *Angew. Chem. Int. Ed. Engl.* **1991**, 30, 1024; *Angew. Chem.* **1991**, 103, 1048; b) M. Ziegler, J. L. Brumaghim, K. N. Raymond, *Angew. Chem. Int. Ed.* **2000**, 39, 4119; *Angew. Chem.* **2000**, 112, 4285; c) P. Mal, B. Breiner, K. Rissanen, J. R. Nitschke, *Science* **2009**, 324, 1697.
- [5] T. Sawada, M. Yoshizawa, S. Sato, M. Fujita, *Nat. Chem.* **2009**, 1, 53.
- [6] a) M. Yoshizawa, T. Kusakawa, M. Fujita, S. Sakamoto, K. Yamaguchi, *J. Am. Chem. Soc.* **2001**, 123, 10454; b) M. Yoshizawa, M. Tamura, M. Fujita, *Science* **2006**, 312, 251.
- [7] a) D. T. Bong, T. D. Clark, J. R. Granja, M. R. Ghadiri, *Angew. Chem. Int. Ed.* **2001**, 40, 988; *Angew. Chem.* **2001**, 113, 1016; b) J. D. Hartgerink, T. D. Clark, M. R. Ghadiri, *Chem. Eur. J.* **1998**, 4, 1367; c) R. J. Brea, L. Castedo, J. R. Granja, *Chem. Commun.* **2007**, 3267; d) W. S. Horne, C. D. Stout, M. R. Ghadiri, *J. Am. Chem. Soc.* **2003**, 125, 9372; e) J. Montenegro, C. Vázquez-Vázquez, A. Kalinin, K. E. Geckeler, J. R. Granja, *J. Am. Chem. Soc.* **2014**, 136, 2484.
- [8] S. J. Dalgarno, G. W. V. Cave, J. L. Atwood, *Angew. Chem. Int. Ed.* **2006**, 45, 570; *Angew. Chem.* **2006**, 118, 584.
- [9] N. Sakai, J. Mareda, S. Matile, *Acc. Chem. Res.* **2008**, 41, 1354.
- [10] N. Ponnuswamy, A. R. Stefankiewicz, J. K. Sanders, G. D. Pantoş, *Top. Curr. Chem.* **2012**, 322, 217.
- [11] a) D. Račkauskaitė, K.-E. Bergquist, Q. Shi, A. Sundin, E. Butkus, K. Wärnmark, E. Orentas, *J. Am. Chem. Soc.* **2015**, 137, 10536; b) Q. Shi, K.-E. Bergquist, R. Huo, J. Li, M. Lund, R. Vácha, A. Sundin, E. Butkus, E. Orentas, K. Wärnmark, *J. Am. Chem. Soc.* **2013**, 135, 15263; c) E. Orentas, C. J. Wallentin, K.-E. Bergquist, M. Lund, E. Butkus, K. Wärnmark, *Angew. Chem. Int. Ed.* **2011**, 50, 2071; *Angew. Chem.* **2011**, 123, 2119; d) S. Stončius, E. Orentas, E. Butkus, L. Öhrström, O. F. Wendt, K. Wärnmark, *J. Am. Chem. Soc.* **2006**, 128, 8272.
- [12] A. Wu, L. Isaacs, *J. Am. Chem. Soc.* **2003**, 125, 4831.
- [13] F. H. Beijer, R. P. Sijbesma, H. Kooijman, A. L. Spek, E. W. Meijer, *J. Am. Chem. Soc.* **1998**, 120, 6761.
- [14] For the only example of the social self-sorting of 3H- and 4H-bonding motifs, see: M. L. Pellizzaro, K. A. Houtona, A. J. Wilson, *Chem. Sci.* **2013**, 4, 1825.
- [15] It is not possible to add or remove an A–B unit from cyclic tetramer [A–B B–A A–B B–A] without disrupting the cyclic structure.
- [16] R. F. Ludlow, S. Otto, *Chem. Soc. Rev.* **2008**, 37, 101.
- [17] a) M. M. Safont-Sempere, G. Fernández, F. Würthner, *Chem. Rev.* **2011**, 111, 5784; b) M. Lal Saha, M. Schmittel, *Org. Biomol. Chem.* **2012**, 10, 4651.
- [18] a) W. Jiang, H. D. F. Winkler, C. A. Schalley, *J. Am. Chem. Soc.* **2008**, 130, 13852; b) W. Jiang, C. A. Schalley, *Proc. Natl. Acad. Sci. USA* **2009**, 106, 10425; c) Z. He, W. Jiang, C. A. Schalley, *Chem. Soc. Rev.* **2015**, 44, 779.
- [19] At this point, it is impossible to confirm that all possible tetrameric aggregates were indeed formed. However, we presented them all to highlight the complexity of the mixture. Also, we used the term mixing to describe the non-selective exchange of monomers between cyclic aggregates.

Received: September 7, 2015

Revised: October 11, 2015

Published online: November 5, 2015