Shape-persistent macrocycle with a self-complementary recognition pattern based on diacetylene-linked alternating hexylbenzene and perfluorobenzene rings†

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The synthesis and characterization of a shape-persistent macrocycle, consisting of alternating electron rich and electron poor sub-units as a self-complementary recognition pattern, is reported, and its increased tendency to form dimer complexes in solution is demonstrated and discussed.

Shape-persistent macrocycles (SPMs) have attracted considerable attention due to their unique properties.[1] Their ability to control the spatial arrangement of functional groups, together with their aggregation behavior, make them promising building blocks for tailor-made nanoscale objects and materials. Since Moore and co-workers reported the aggregation of SPMs due to π-stacking,[2] the phenomenon has been investigated in detail with further functionalized SPMs. In particular, electron donating[3] and electron withdrawing[4] substituents,[2,5] hydrogen bonding units,[6] chiral building blocks[7] and even coordination sites for metal ions[8] have been incorporated into SPMs, and their aggregation properties have been studied in detail.

To further increase the intramolecular aggregation, we designed macrocycle **1**, consisting of diacetylene-linked alternating electron rich alkylbenzene and electron deficient tetrafluorobenzene units in a self-complementary recognition pattern (Fig. 1). The π–π stacking interaction between benzene and hexafluorobenzene was reported in 1960 by Patrick and Prosser.[9] The supramolecular synthon has meanwhile been investigated in detail and has been applied successfully in crystal engineering,[10] surface patterning,[11] topochemistry[12] and even to pre-organize reactants.[13] Furthermore, the synthon allowed the tuning of the material properties of liquid crystals,[14] polymers,[14] hydrogels[15] and even biomolecules such as DNA duplexes.[16]

Several macrocyclic oligomers consisting of diacetylene-linked aromatic units have been synthesized by oxidative acetylene coupling protocols, often in combination with protection group strategies.[4,5,17] However, for the assembly of the macrocyclic target structure with two different aromatic units, a Cadiot–Chodkiewicz coupling,[18] allowing the formation of asymmetric diacetylenes, has been chosen. As displayed in Scheme 1, the tetrafluorobenzene unit **4** was functionalized with bromoacetylenes, and the hexylbenzene unit was synthesized as mono-protected and unprotected diacetylenes **8** and **9**, respectively, as modular precursors of the macrocycle **1**.

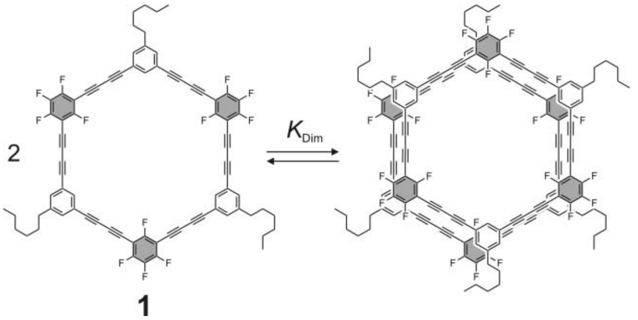

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Fig. 1 Macrocycle **1**, providing an alternating sequence of electron rich and electron poor aromatic units as self-complementary recognition pattern, and its aggregation to a dimer.

Reduction of commercial tetrafluoroisophthalonitrile provided tetrafluoroisophthaloaldehyde **2** in 45% yield.[17c] In a Corey–Fuchs reaction sequence,[19] the dialdehyde **2** was converted into the doubly dibromoethenyl-functionalized precursor **3**, which was isolated in 92% yield after column chromatography (CC) as a white solid. Treatment of **3** with a strong base provided the doubly bromoethynyl-substituted tetrafluorobenzene **4** as a white solid after CC in 94% yield as the first building block for the assembly of macrocycle **1**.

Bromination of 4-hexylaniline with *N*-bromosuccinimide in DMF afforded 2,6-dibromo-4-hexylaniline (**5**) in 85% yield after CC as a red crystalline solid. Deamination of **5** with sodium nitrite in sulfuric acid and ethanol provided 1,3-dibromo-5-hexylbenzene (**6**) in 67% yield as a colorless oil. Both bromines of **6** were substituted by tris-*iso*-proylsilyl (TIPS) acetylenes in a Sonogashira coupling reaction[20] to yield the TIPS-protected diacetylene **7** in 85% as a colorless oil. Careful deprotection of **7** with TBAF in wet THF provided (besides unreacted starting material) the mono-protected diacetylene **8** in 27% yield and the diacetylene **9** in 18% yield, both as colorless oils as the unfluorinated building blocks of **1**.

For the formation of macrocycle **1**, several strategies, varying in the number of assembled molecules and formed bonds, were envisaged and have been investigated. Already, a 1 : 1 mixture of diacetylene **9** and di(bromoacetylene) **4** may result in the desired macrocycle **1** by the assembling of 6 molecules. However, only

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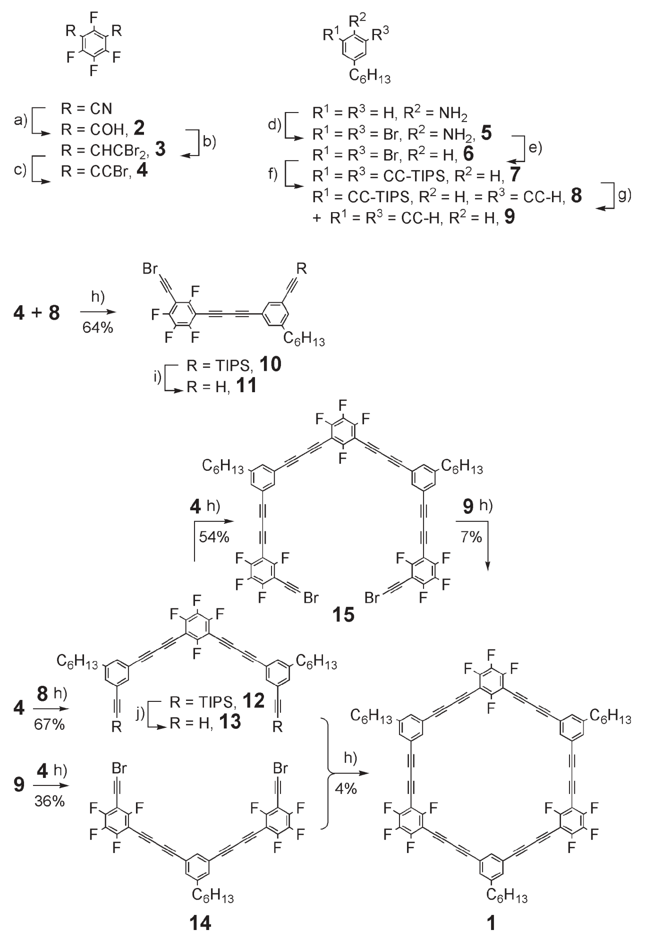

Scheme 1 Synthesis of the macrocycle **1** and its precursors **2–15**.† (a) Toluene, DIBAL-H, rt, 45%; (b) CBr_4, Zn, PPh_3, CH_2Cl_2, rt, 92%; (c) aq. KOH, BTEAC, THF, rt, 94%; (d) NBS, DMF, 0 °C, 85%; (e) H_2SO_4, $NaNO_2$, EtOH, 75 °C, 68%; (f) $Pd(PPh_3)_4$, Et_3N, CuI, TIPS-CCH, 80 °C, 85%; (g) TBAF, wet THF, rt, 27% for **8**, 18% for **9**; (h) $Pd_2(dba)_3\cdot CHCl_3$, $(i\text{-}Pr)_2EtN$, CuI, toluene, rt; (i) TBAF, wet THF, AcOH until pH 7.5, rt, 5%; (j) TBAF, wet THF, rt, 79%.

traces of the desired macrocycle were formed, together with a rich variety of side products. To assemble the macrocycle in a stepwise approach and to optimize the Cadiot–Chodkiewicz coupling conditions, di(bromoacetylene) **4** was coupled with mono-protected diacetylene **8** to provide the promising precursor, **11**, of the macrocycle. In a Pd/Cu-catalyzed variation of the Cadiot–Chodkiewicz coupling,[21] the mono-protected diacetylene **8** was treated with a two-fold excess of **4** in THF using di-*iso*-propylethylamine ($(i\text{-}Pr)_2NEt$) as a base, and $Pd_2(dba)_3$ and CuI as catalysts at room temperature to provide the TIPS-protected molecular rod **10** in 64% yield after CC.

However, the deprotection of **10** turned out to be very delicate due to the limited stability of the bromoacetylene of **10** in basic TBAF/THF conditions and the limited stability of the perfluorinated benzene ring under AcOH-buffered TBAF/THF conditions. The low yield of 5% of the isolated precursor **11** considerably reduced the attractiveness of this synthetic route. Macrocycle **1** may also be assembled from two semicircles. However, due to the three-fold symmetry of **1**, two different building blocks, **13** and **14**, are required. As displayed in Scheme 1, both semicircles are assembled in reasonable yields by applying the above described Pd/Cu-catalyzed Cadiot–Chodkiewicz protocol. Treatment of di(bromoacetylene) **4** with two equivalents of mono-protected diacetylene **8** provided the semicircle **12**, comprising terminally TIPS-protected acetylenes, in 67% yield. Subsequent deprotection with TBAF/THF yielded the acetylene-functionalized semicircle **13** in 79% yield. To assemble the semicircle with terminal bromoacetylenes, the coupling conditions were applied to a mixture of diacetylene **9** and an excess of di(bromoacetylene) **4**. The desired building block **14** was isolated in 36% yield after CC. Again, applying the Pd/Cu-catalyzed coupling conditions to a 1 : 1 mixture of **13** and **14** afforded the desired macrocycle in 4% yield as a brown solid after laborious CC, including size exclusion chromatography (SEC).

In an alternative strategy, the semicircle **13** was extended to the terminally bromoacetylene-functionalized pentamer **15** by treating **13** with a seven fold excess of **4**. Pentamer **15** was isolated in 54% yield as beige-brown solid after CC. Subsequently, the macrocycle was closed by introducing diacetylene **9** into pentamer **15**. The target structure **1** was isolated in 7% yield after SEC. Inspite of the slightly lower yield over both steps, the considerably simpler and more efficient isolation procedure for the macrocycle **1** synthesized *via* the pentamer **15** route favors this synthetic strategy.

The structure of macrocycle **1** and its precursors were characterized by ^1H and ^{13}C NMR spectroscopy, mass spectrum analysis and elemental analysis. The rather simple NMR spectra of **1** points to its high structural symmetry. While the ^1H NMR is not particularly rich in structural information, characteristic features of the ^{13}C NMR spectrum of **1** are the typically large C–F couplings, in the order of 250 Hz, of the fluorine-substituted benzene carbons and the four acetylene carbons at 66.1, 74.6, 81.4 and 84.5 ppm, respectively. An intense signal for the molecular ion was observed by electron spray ionization mass analysis. Interestingly, MALDI-TOF MS failed to detect the molecular ion. Instead, intense signals have been observed for approximately two, three and even higher multiples of its weight (Fig. 2). As larger oligomers formed during the macrocyclization were removed by SEC, these signals, most likely arising from aggregates,[22] already point to a pronounced

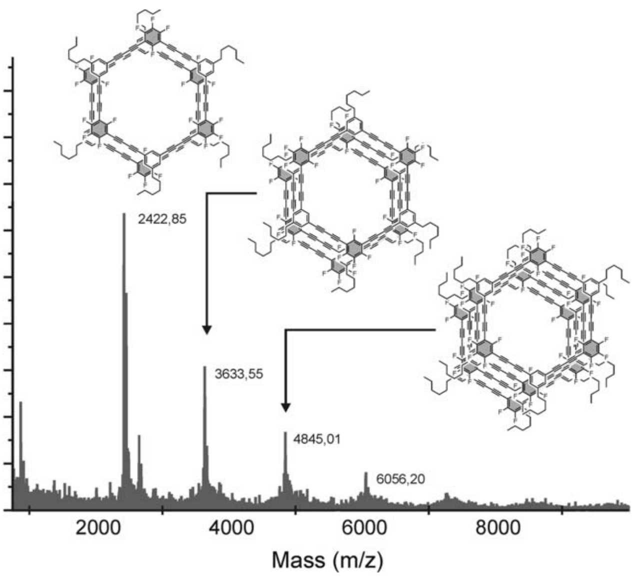

Fig. 2 Oligomeric signals of macrocycle **1** in the MALDI-TOF MS.

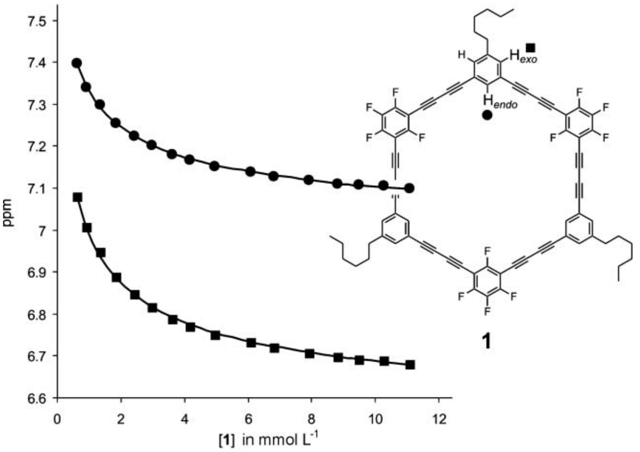

Fig. 3 Chemical shift changes with concentration of the *exo*-annular (■) and *endo*-annular (●) protons of **1** in $CDCl_3$ at 20 °C. The solid lines are the simulated chemical shifts with K_{Dim} = 1875 M^{-1}.

stacking of macrocycle **1** in the solid state of the anthracene triol matrix in the MALDI-TOF MS. Furthermore, the structural motif has been reported to photopolymerize in the solid state,[12a] and thus these oligomeric structures may even be covalently-linked macrocycles formed by photoreactions during ionization. The solubility of macrocycle **1** is limited to aprotic organic solvents, *e.g.* toluene and THF, and is improved in chlorinated solvents like chloroform or dichloromethane. However, even in chloroform, the solution is saturated by about 25 mmol L^{-1}, also pointing to distinctive intermolecular interactions.

Of particular interest were the stacking properties of macrocycle **1** in solution, which were investigated by concentration dependent ^1H NMR experiments and by vapor pressure osmometry (VPO). In the concentration range between 0.5 and 11 mmol L^{-1} in $CDCl_3$, both proton signals of the benzene unit shift asymptotically towards higher field with increasing concentration (Fig. 3).† The upfield shift indicates a face-to-face aggregation of **1**, as reported for the self-association of SPMs due to π–π stacking interactions.[2–7] The signal of the *exo*-annular protons shifts 0.4 ppm, more pronounced than the 0.3 ppm for the *endo*-annular protons in the investigated concentration range at 20 °C. While the intended strong intramolecular π–π stacking interaction was confirmed by the NMR titration experiments, it remained uncertain whether dimers or larger oligomeric stacks were formed in solution.

Only a small concentration window, limited by the sensitivity of the VPO equipment on the one hand and by the solubility of **1** on the other, remained open for VPO investigations. Thus, in the concentration range between 15 and 25 mmol L^{-1}, in which, according to the NMR titration experiments, mainly stacked objects are present, an average molecular weight of 2000 ± 500 was determined by VPO in $CHCl_3$ at room temperature. The measured molecular weight supports the formation of dimers in solution, as sketched in Fig. 1. The ^1H NMR titration data were thus fitted assuming a monomer–dimer equilibrium,[23] in similarity with the already reported investigations of SPM model compounds.[2–6] The obtained dimerization constant (K_{Dim}) for **1** was 1875 ± 605 M^{-1} in $CDCl_3$ at 20 °C, more than one order of magnitude larger than those reported for SPMs consisting of uniform aromatic sub-units. The temperature dependence of K_{Dim} further allowed the determination of thermodynamic data of the self-assembly system by applying van't Hoff analysis.† The negative signs of the obtained $\Delta S = -156 \pm 9$ J mol^{-1} K^{-1} and $\Delta H = -64 \pm 3$ kJ mol^{-1} show that the dimerization of **1** is enthalpy driven.

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