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Multicomponent Dynamic Covalent Assembly of a Rhombicuboctahedral Nanocapsule

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Abstract: Molecular container compounds have a range of potential applications in chemical and biological sciences, most notably as nanoreactors, drug delivery devices, and storage materials. We report a highly efficient dynamic covalent chemistry approach for the synthesis of covalent rhombicuboctahedral nanocapsule **1** from 14 square- and triangular-shaped molecular components. The nanocapsule is obtained in a one-pot reaction in high yield and high purity, and has a solvodynamic diameter of 3.9 nm. In our approach, six formyl cavitands and eight 1,3,5-tris(*p*-aminophenyl)benzene molecules are assembled into a molecular rhombicuboctahedron through twenty four newly formed dynamic imine bonds. Binding studies show that **1** encapsulates tetraalkylammonium salts in toluene. We also discuss the growth mechanism of this nanocapsule.

Keywords: dynamic covalent chemistry · host–guest systems · multicomponent reactions · nanostructures · supramolecular chemistry

Introduction

Molecular container compounds are hollow nanospheres that allow the encapsulation of one or more guest molecules and insulate them from the bulk phase.[1–4] They have received much attention from the chemical community, in part owing to their potential application as nanoreactors in which otherwise fleeting reactive intermediates become persistent,[5] reactions are accelerated,[6–9] and regiochemistry and selectivity are altered.[10–11] The development of self-assembly processes that involve hydrogen bonding and transition metal coordination chemistry has allowed the synthesis of nanometer-sized capsules with remarkably high efficiencies.[2–4,12,13] Recently, multistep approaches towards the formation of covalent nanocapsules have also been devised.[14–15] This report demonstrates the highly efficient covalent synthesis of nanocapsule **1** by using dynamic covalent chemistry,[16,17] which is advantageous for the multicomponent synthesis of structurally and topologically highly complex molecules by combining covalent bond formation with the virtues of self-assembly processes, such as error correction and proof reading.[18,19]

Our approach towards the efficient synthesis of a nanosphere involves using two different 2D panels,[2,13a] which upon selection of an appropriate dynamic connector are precisely arranged in space such that the assembly has a high propensity to grow into the desired structure even in the absence of templates. The angle between the square created by connecting the four formyl-substituted aryl carbons of cavitand **2** and an aryl–formyl bond is approximately 120°, which matches that between corner-connected triangular and square faces in a rhombicuboctahedron. Herein, we show that a nanometer-sized molecular rhombicuboctahedron can be prepared in high yield and high purity in a one-pot reaction through the thermodynamically controlled condensation of six square-shaped cavitands (**2**) and eight triangular panels (**3**, Scheme 1).

Results and Discussion

The slow addition of eight equivalents of tris(*p*-aminophenyl)benzene **3** to a solution of six equivalents of cavitand **2** in chloroform that contained catalytic amounts of trifluoroacetic acid (TFA) gave a complex product mixture, which contained hexamer **1** (10%) and small amounts of dimer **4**.

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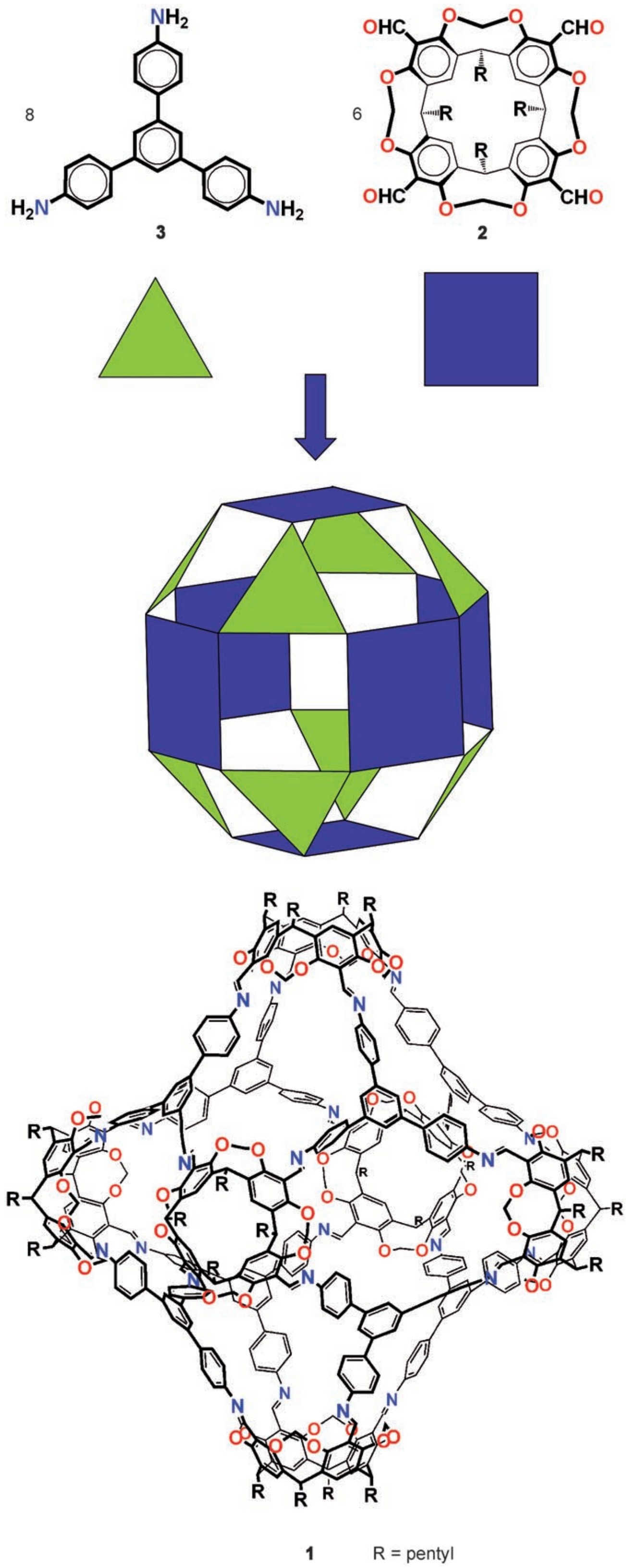
This mixture remained essentially unchanged, which indicated very slow imine bond exchange, and turned into polymeric aggregates when heated ($M_r > 25$ kD). However, upon slow addition of excess amounts of **3**, all species equilibrated within two days into a mixture of **1** and **4**, of which the latter quantitatively precipitated. Simple filtration of the reaction mixture through a pad of triethylamine-deactivated silica gel gave **1** in essentially analytically pure form in a yield of 60 to 70%. Unreacted **3** (80% recovery) and **4** (15–30% yield) were isolated by subsequently washing the silica gel with ethyl acetate to elute **3**, and with toluene in which dimer **4** is sparingly soluble.

Hexamer **1** can be compared with a rhombicuboctahedron (Scheme 1), which is one of the Archimedean solids. The six cavitands and eight triphenylbenzene molecules occupy the squares along the C_4 axes and the triangular faces, respectively, and the imino groups correspond to the twenty four vertices of the rhombicuboctahedron. The identity of **1** is supported by NMR spectroscopy and mass spectrometry analyses. In the MALDI-TOF mass spectrum of **1**, the major ion signal at m/z 7955.2 was assigned to the protonated form of **1** (calcd m/z 7954.8). The simplified ^{1}H and ^{13}C NMR spectra of **1** are also consistent with the proposed structure and O_h symmetry. For example, only one singlet at



Scheme 1. Covalent assembly of molecular rhombicuboctahedron **1** from six square panels (**2**) and eight triangular panels (**3**).

Abstract in German: *Molekulare Containerverbindungen bieten zahlreiche Anwendungsmöglichkeiten in der chemischen und biologischen Forschung insbesondere als Nanoreaktoren, Wirkstofftransportsysteme und zur Gasspeicherung. Wir beschreiben hier ein auf dynamisch kovalenter Chemie beruhendes, sehr effizientes Verfahren zur Synthese einer rhombicuboktaedrischen Nanokapsel **1**, die aus 14 quadratischen und dreieckigen Komponenten aufgebaut ist und einen Durchmesser von 3.9 nm besitzt. Kapsel **1** bildet sich in hoher Ausbeute und Reinheit durch Kondensation von 6 Formylcavitanden und 8 1,3,5-Tris(p-aminophenyl)-benzolen, wobei 24 neue Iminbindungen geknüpft werden. Bindungsstudien zeigen, dass 1 Tetraalkylammonium Salze in Toluol einschliesst. Weiterhin diskutieren wir den Kapselbildungsmechanismus.*

Abstract in Chinese:

分子容器化合物在化学和生物科学领域具有一定的应用前景，特别是作为纳米反应器、药物运载装置和储存材料。我们报道了一种非常有效地从 14个平面型及三角型分子来合成一个斜方立方八面体纳米容器（1）的动态共价键化学途径。这个通过一锅反应高产率高纯度合成的纳米分子容器具有溶剂动力直径 3.9 nm。6 个甲酰基碗状分子和8个1,3,5－三取代（对氨基苯基）苯分子通过24个新形成的动态亚胺键组装成这个斜方立方八面体纳米分子容器。主客体络合实验表明 1 在甲苯中配合四烷基铵盐。我们还讨论了这个纳米分子容器的形成机理。

$\delta = 8.77$ ppm was observed for the twenty four equivalent imine protons (Figure 1). The size of this nanosphere was estimated from its diffusion properties. A DOSY experiment

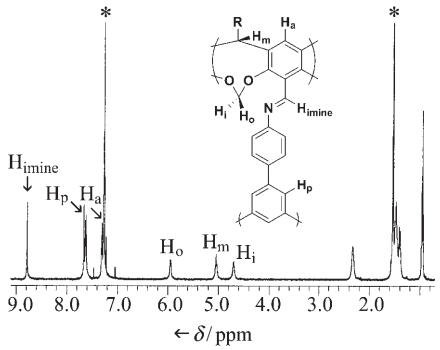


Figure 1. ^{1}H NMR spectrum (500 MHz, $CDCl_3$, 25 °C) of **1**. Selected signals are labeled. Solvent peaks are marked with asterisks.

provided a diffusion constant of $(2.08 \pm 0.05) \times 10^{-6}$ cm^2 s^{-1} in $CDCl_3$ at 25 °C,[20] from which we calculated a solvodynamic diameter of 3.9 nm by using the Einstein–Stokes equation for diffusion of spherical molecules. This dimension is consistent with molecular mechanical calculations that predict a nanosphere torso with a cavity diameter of 3 nm and an inner cavity volume of approximately 4700 Å^3 (Figure 2).[21]

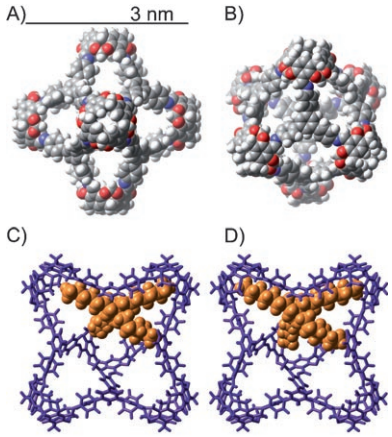


Figure 2. Space-filling models of the energy-minimized structure of **1** with appended pentyl groups replaced by hydrogen atoms (MM3,[22] gas phase, C: gray, H: white, O: red, N: blue). View along the C_4 (A) and C_3 axes (B). Energy-minimized structures (MM3,[22] gas phase) of one tetraheptylammonium molecule (C) and one tetraoctylammonium molecule (D) encapsulated inside **1** (blue). Part of **1** has been removed for clarity.

The eight larger openings in the host shell are elliptically shaped ($\approx 7 \times 9$ Å) and should allow the easy entry of solvent and small or medium-sized organic molecules. Although suitable crystals for diffraction studies could not be obtained, NOE data for **1** are fully consistent with the structure shown in Figure 2.

Preliminary binding studies show that **1** encapsulates tetraalkylammonium salts. Addition of up to one hundred equivalents of $(n\text{-octyl})_4$NBr led to the encapsulation of two ion pairs, as determined from the integration of a new set of upfield-shifted guest signals, which we assigned to encapsulated $(n\text{-octyl})_4$NBr in slow exchange with free guest (Figure 3D–F). The observation of signals for ions [**1**·{(n-octyl)$_4$N}$_2$Br]$^+$ and [**1**·(n-octyl)$_4$N]$^+$ in the MALDI-TOF mass spectrum of this solution further supported our conclusion (Figure S8 in the Supporting Information). An estimate of the packing coefficient of 0.25 for **1**·2(n-octyl)$_4$NBr) suggests that the two molecules of $(n\text{-octyl})_4$NBr are coencapsulated with solvent molecules, which are in rapid exchange with the bulk.[23] The smaller molecule $(n\text{-heptyl})_4$NBr showed weaker binding. Addition of $(n\text{-heptyl})_4$NBr to a solution of **1** in [D_8]toluene led to a strong broadening of several host signals, especially those assigned to the triphenylbenzene units and the outwardly pointing acetal protons of the cavitand (H_o, Figure 3A–C). In addition, a new strongly broadened signal at $\delta = -0.2$ ppm started to build up at high guest concentrations ([(n-heptyl)$_4$NBr]/[**1**] = 4:1, Figure 3B, C). We

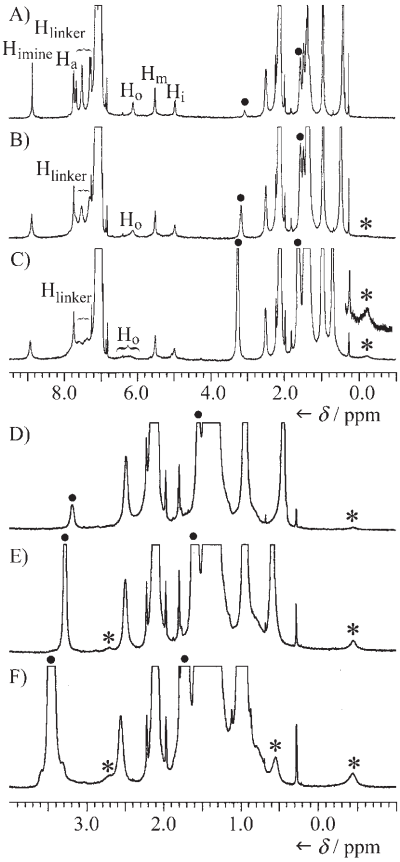


Figure 3. ^{1}H NMR spectra of **1** (500 MHz, [D_8]toluene) in the presence for (n-C_7H_{15})$_4$NBr (1 equiv, A), (4 equiv, B), and (20 equiv, C) and (n-C_8H_{17})$_4$NBr (2 equiv, D), (10 equiv, E), and (100 equiv, F). Selected signals of encapsulated (*) and free (●) tetraalkylammonium bromide are indicated.

assigned this signal to the methyl protons of encapsulated (n-heptyl)$_4$NBr. The remaining signals of the encapsulated guest could not be identified owing to overlap with host and free guest signals. At the highest guest concentration ([(n-heptyl)$_4$NBr] = 5 mM = 70 equiv), on average one guest is complexed. Encapsulation of larger tetraalkylammonium ions ((n-$C_{14}H_{29}$)$_4$NBr, (n-$C_{16}H_{33}$)$_4$NBr, or (n-$C_{18}H_{37}$)$_4$NBr) failed under the same conditions despite the fact that the cavity of **1** is large enough to accommodate at least one of these ion pairs. Presumably, the openings in the shell of the host are too small to allow guest entry at room temperature and/or the affinity for these ion pairs is simply too low.

Analysis of the binding isotherm for (n-octyl)$_4$NBr complexation by using a 2:1 binding model with independent binding sites and no cooperativity (statistical binding) gave binding constants of $K_1 = 10^{(3.6\pm0.1)}\,\mathrm{M}^{-1}$ and $K_2 = 10^{(3.0\pm0.1)}\,\mathrm{M}^{-1}$.[24,25] A similar analysis for the complexation of (n-heptyl)$_4$NBr was not possible owing to strong broadening of encapsulated guest signals at high guest concentrations, which precluded proper integration. We propose that (n-octyl)$_4$NBr is more strongly bound in **1** than (n-heptyl)$_4$NBr owing to a better fit within the cavity. Force field calculations show that the two methyl groups of (n-octyl)$_4$N$^+$ can interact nicely with two adjacent cavitands of **1** if the octyl chains are fully extended (Figure 2D). The shorter heptyl chains only allow one methyl–cavitand interaction at a time (Figure 2C), which leads to a more unfavorable enthalpy of binding. Consistently, a larger average complexation-induced upfield shift was observed for (n-octyl)$_4$NBr ($\Delta\delta = 1.45$) than (n-heptyl)$_4$NBr ($\Delta\delta = 1.18$). We believe that partial or full desolvation of the inner surfaces of **1** and (n-octyl)$_4$NBr, which is associated with a large favorable entropy term towards the free energy of binding, drives the encapsulation of both guests.[23,26] Consistently, the amount of encapsulated guests decreased upon lowering the temperature.

A mass spectrometric and gel permeation chromatographic (GPC) analyses of the condensation reaction between **2** and **3** gave additional insight into the nanocapsule growth mechanism (Figure 4, Scheme 2). This study supports a stepwise growth that involves four- (tetramers) and five-cavitand (pentamers) assemblies as major intermediates. The slow addition of the first four of twelve equivalents of **3** to six equivalents of **2** initially leads to a mixture of tetramers and pentamers (Figure 4A, B). MALDI-TOF mass spectra show that the distribution of tetramers and pentamers is very narrow and that the major tetrameric (**T**) species is an assembly of four cavitands plus four tris(p-aminophenyl)benzene molecules linked by twelve imine bonds and the pentameric species (pentamer **I**) is an assembly of five cavitands plus six tris(p-aminophenyl)benzene molecules linked by eighteen imine bonds (Figure 5). Both are particularly stable intermediates because **T** is already a major constituent of the reaction mixture after only two equivalents of **3** have been added (Figure 4A). Further addition of the remaining eight equivalents of **3** followed by an equilibration period converts almost all of the tetramers into pentamers (Figure 4C–E). The composition remained almost unchanged upon longer equilibration. However, addition of a large excess of **3** as a transimination catalyst triggers a rapid conversion of the pentamers into **1** (Figure 4F, G).[16] According to our GPC analysis, this conversion involves an association–disproportionation mechanism (Scheme 2). In the presence of excess **3**, pentamer **I** is converted into pentamer **II**, which is composed of five cavitands and eight triamine molecules linked by twenty imine bonds and has free amino groups (Figure 6). The most logical structure of pentamer **II** is a hexamer that lacks one cavitand unit. Two pentamer **II** units fuse together through one or more transimination reactions to form decameric intermediates (see the Supporting Information), which have enough building blocks to yield **1**. Although the exact mechanism of the breakdown of these decamers into **1** is not known, it must involve multiple transiminations that eventually lead to **1** by subsequent splitting to produce two dimers or a tetrameric fragment, which under these conditions primarily breaks down to form two dimers. The GPC peak area of **1** and **4** consistently remain at an approximate ratio of 2:1 as long as pentamer **II** and decamers are observed in the reaction mixture.

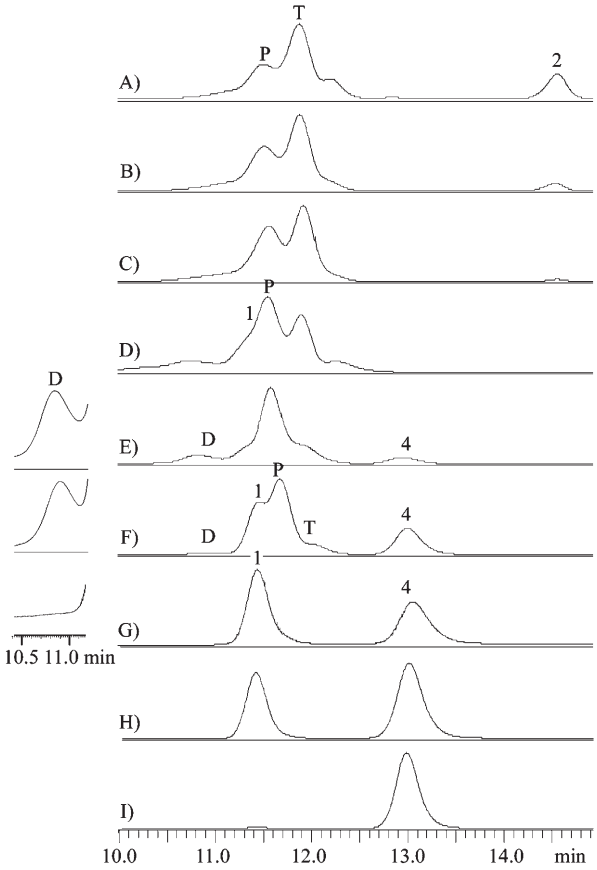
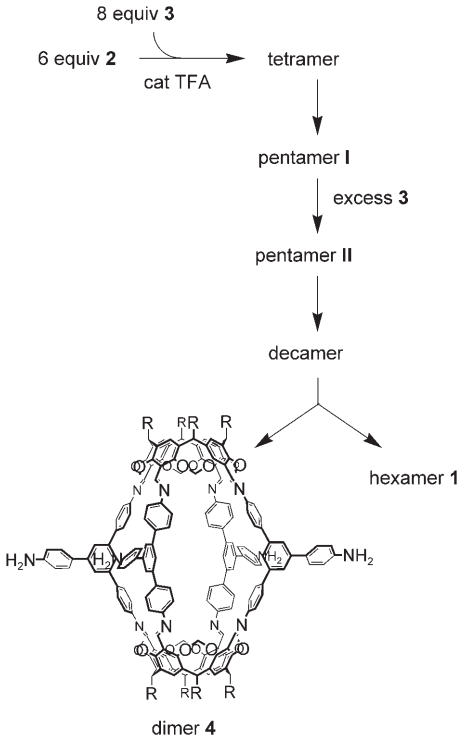


Figure 4. GPC traces of products formed during the slow addition of **3** (12 equiv) to **2** (6 equiv) in the presence of catalytic TFA followed by equilibration before and after addition of a large excess of **3**. Immediately after slow addition of **3** for 2 (A), 4 (B), 6 (C), and 9 equiv (D). Addition of **3** (12 equiv) followed by equilibration for E) 12 h, F) 2 h, G) 22 h, H) 3 days, and I) 5 days. Peaks assigned to tetramer, pentamer and decamer intermediates are labeled with **T**, **P**, and **D**, respectively.



Scheme 2. Proposed association–disproportionation mechanism for the formation of **1** in the TFA-catalyzed condensation of **2** with **3**.

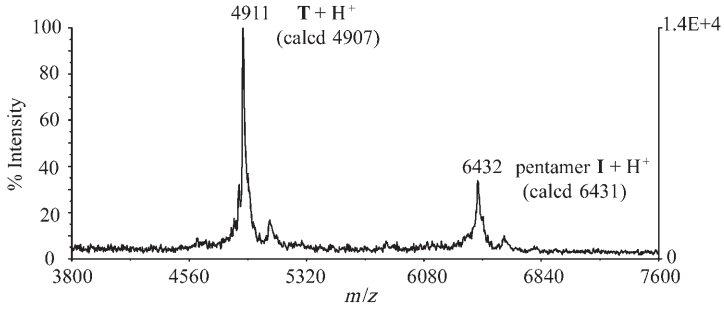


Figure 5. Low resolution MALDI-TOF mass spectrum of the reaction mixture that contains **T** and pentamer **I** (see GPC trace Figure 4B, matrix: 2,4,6-trihydroxyacetophenone). A good match between the observed and calculated m/z values is observed for a $4\times\mathbf{2}+4\times\mathbf{3}$ assembly, in which the components are linked by 12 imine bonds (**T**: calcd for $[\mathbf{T}+H]^+$: m/z: 4907) and a $5\times\mathbf{2}+6\times\mathbf{3}$ assembly held together by 18 imine bonds (pentamer **I**: calcd for [pentamer $\mathbf{I}+H]^+$: m/z: 6431).

Further support for the proposed association–disproportionation growth mechanism comes from the following observations: 1) cavitand species are not observed during the equilibration, which makes stepwise growth of a smaller intermediate by fusion with a cavitand unlikely; 2) during the entire period in which the hexamer concentration increases, a small steady-state concentration of decamers is observed (Figure 4E–G); and 3) if the reaction is carried out at a higher dilution of polycavitand intermediates, but with an identical concentration of free **3** (saturation), then the concentration of decamers and the conversion rate of the pentamer to the hexamer are decreased.

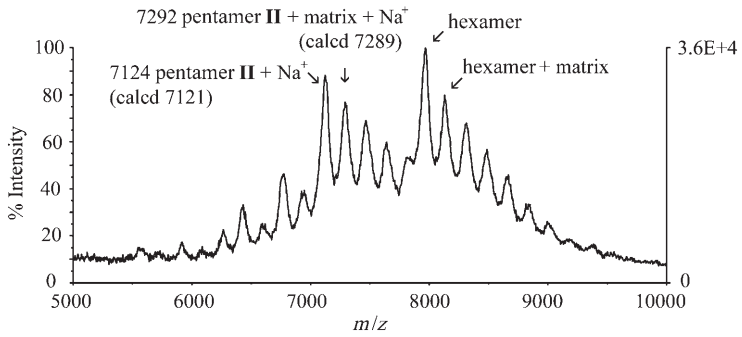


Figure 6. Low resolution MALDI-TOF mass spectrum of a mixture that contains pentamer **II** and hexamer **1** (matrix: 2,4,6-trihydroxyacetophenone).

Upon increasing the reaction time, **1** slowly converts into **4**. The equilibrium shift is likely to be driven by mass law owing to the insolubility of **4** in chloroform, and may not be as a consequence of a higher stability of **4** than **1**. In fact, **1** is more stable than **4** if the condensation reaction is carried out with stoichiometric amounts of **3** and aniline **5** as the transimination catalyst.[27] Addition of two equivalents of **5** instead of an excess of **3** led to an equilibrium composed of hexamers and tetraiminocavitands without the formation of dimers (see the Supporting Information). Nevertheless, the use of **5** as a transimination catalyst did not prove to be practical for the preparation of **1**. To achieve equilibration in a reasonable time (<1 week), high concentrations of TFA (>0.15 equiv per CHO) are required, which leads to substantial cleavage of OCH_2O groups of the cavitand building blocks.[28]

We rationalize the higher thermodynamic stability of **1** than **4** under the latter conditions with the higher ratio of intra- to intermolecular imine bonds in **1**. This results in a higher average effective molarity for intramolecular condensations that lead to **1** and, according to Ercolani's theoretical model of multicomponent nanocage self-assembly, to a higher equilibrium concentration of **1** than **4**.[29–32]

Conclusion

The dynamic covalent synthesis of nanocapsule **1** complements earlier nanocapsule syntheses that use reversible Schiff base chemistry.[17] Contrary to earlier work, the use of two 2D building blocks (cavitand **2** and trigonal, planar triamine **3**) in the current approach yields a pure nanocapsule in a high yield, thus allowing simple scale-up. We predict that this design principle will be widely applicable to allow the preparation of other nanospheres from different square and triangular building blocks. Features that are characteristic of **1**, such as a reinforced structure and a large number of aryl units facing the inner cavity, have proven to be very beneficial for the molecular recognition properties of metal

coordination capsules,[2,13a,b] which bind organic guest molecules with high affinity despite having openings that allow the movement of guests in and out of the capsules with little steric hindrance. Water-soluble derivatives of **1** are expected to show similar interesting recognition properties. The large cavity volume of almost 5000 Å^3 combined with the metal-free synthesis suggests new opportunities for applications, especially in biochemical and biomedical research.

Experimental Section

General: All reactions were conducted under argon. Reagents and chromatography solvents were purchased from Aldrich and used without further purification, apart from chloroform, which was passed through K_2CO_3 prior to use. ^{1}H NMR spectra recorded in $CDCl_3$ or [D_8]toluene were referenced to residual $CHCl_3$ and [D_8]toluene at 7.26 and 2.09 ppm, respectively. ^{13}C NMR spectra recorded in $CDCl_3$ were referenced to $CDCl_3$ at 77.0 ppm. NMR spectra were recorded on VARIAN 500 and 400 NMR instruments. Mass spectra were recorded by using an Applied Biosystems Voyager DE-Pro mass spectrometer (MALDI-TOF) with 2,4,6-trihydroxylacetophenone (THAP) as the matrix. Positive molecular ions were usually detected as proton or sodium adducts for the compounds reported herein. Gel permeation chromatography (GPC) was performed by using a Thermo SpectraSYSTEM HPLC system equipped with a dual wavelength UV/Vis detector (280 nm), an Eppendorf CH-30 column heater, and two Jordi GPC columns (cross-linked DVB, 10^3 Å pore size, M_r cutoff ≈25,000, 7.8 mm × 30 cm) with CH_2Cl_2/1 % NEt_3 as the mobile phase at a flow of 1 mL min^{-1}. Approximate molecular weights of analytes were determined from a semilogarithmic calibration plot (Ln(M_r) against retention time) by using the following molecular weight standards: benzene (M_r 78), cavitand **2** (M_r 928), an NMP hemicarceplex (M_r 2348),[33] and three polyaminonanocapsules (M_r 3941, 5912, and 7882).[17] Samples of reaction mixtures that contained precipitated **4** were diluted with toluene until **4** had completely dissolved.

1,3,5-Tris-(*p*-aminophenyl)benzene 3: Compound **3** was prepared according to a literature procedure.[34] Crude **3** was further purified by column chromatography (SiO_2, 2.5 v % MeOH/CH_2Cl_2).

Compounds 1 and 4: A solution of **3** (95.0 mg, 0.271 mmol) in $CHCl_3$ (30.0 mL) was added to a solution of cavitand **2** (102 mg, 0.110 mmol)[35] and TFA (0.87 μL, 0.0117 mmol) in $CHCl_3$ (8.0 mL) with a syringe pump over 14 h. Additional **3** (80.0 mg, 0.228 mmol) was added into the reaction mixture 8 h after the slow addition had finished.[36] After 2 d, the mixture was passed through a silica gel plug soaked with 5 vol % NEt_3 in chloroform. The product was washed out with a solution of 5 vol % NEt_3/$CHCl_3$. The filtrate was concentrated down under reduced pressure and the residue was dried in high vacuum line at room temperature overnight. A deep yellow solid **1** was obtained (95.0 mg, 65 % yield based on the cavitand **2**). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 8.77 (s, 24 H; H_{imine}), 7.66 (s, 24 H; H_{aryl}), 7.62 (d, J = 8.22 Hz, 48 H; H_{aryl}), 7.31 (s, 24 H; H_{aryl}), 7.25 (d, J = 8.83 Hz, 48 H; H_{aryl}), 5.92 (d, J = 6.35 Hz, 24 H; H_{outer}), 5.03 (t, J = 7.62 Hz, 24 H; $H_{methine}$), 4.69 (d, J = 6.63 Hz, 24 H; H_{inner}), 2.32 (br s, 48 H), 1.54–1.35 (m, 144 H), 0.95 ppm (t, 72 H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 155.0 (C12), 153.9 (C10), 151.4 (C13), 142.0 (C17), 139.40 (C16), 138.9 (C9), 128.2 (C15), 125.0 (C18), 123.6 (C11), 122.3 (C8), 121.4 (C14), 100.4 (C7), 36.5 (C6), 32.0 (C4), 29.8 (C5), 27.6 (C3), 22.7 (C2), 14.1 ppm (C1); IR (NaCl): $\tilde{\nu}$ = 2957, 2931, 2859, 1622, 1600, 1580, 1503, 1468, 1448, 1359, 1242, 980 cm^{-1}; MALDI-TOF MS: m/z: 7955.2 [M+H$^+$]; elemental analysis calcd (%) for $C_{528}H_{504}N_{24}O_{48}$: C 79.73, H 6.39, N 4.23; found: C 79.29, H 6.34, N 4.22.

The silica gel plug was washed with ethyl acetate (100 mL) to remove excess **3**. Subsequently, dimer **4** was eluted with toluene (100 mL). The filtrate was concentrated and dried to yield **4** as a pale yellow solid (60.0 mg, 35 %). ^{1}H NMR (500 MHz, [D_8]toluene, 25 °C): δ = 8.82 (s, 8 H; H_{imine}), 7.76 (s, 8 H; H_{aryl}), 7.71 (s, 8 H; H_{aryl}), 7.52 (s, 4 H; H_{aryl}), 7.48 (d, J = 8.17 Hz, 16 H; H_{aryl}), 7.38 (d, J = 8.17 Hz, 8 H; H_{aryl}), 7.19 (d, J = 8.37 Hz, 16 H; H_{aryl}), 6.35 (d, J = 8.41 Hz, 8 H; H_{aryl}), 5.85 (d, J = 7.72 Hz, 8 H; H_{outer}), 5.46 (t, J = 7.80 Hz, 8 H; $H_{methine}$), 4.94 (d, J = 7.20 Hz, 8 H; H_{inner}), 2.84 (s, 8 H; NH_2), 2.46 (m, 16 H), 1.53–1.37 (m, 48 H), 0.95 ppm (t, 24 H); MALDI-TOF MS: m/z: 3117.79 [M+H$^+$].

Acknowledgements

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