Supramolecular Chemistry

DOI: 10.1002/ange.200504049

One-Pot, 18-Component Synthesis of an Octahedral Nanocontainer Molecule**

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The investigation and application of molecular container compounds is a main focus in host–guest chemistry.[1] Molecular containers permit the room-temperature stabilization of otherwise fleeting intermediates,[2] accelerate reactions, and change regio- and stereochemistry.[3,4] The development of self-assembly processes for the synthesis of molecular capsules involving hydrogen bonding or metal coordination has tremendously spurred the growth of this field.[5–8] The power of these supramolecular approaches is their ease and efficiency, best demonstrated in the quantitative synthesis of nanoscale capsules that are large enough to accommodate multiple guests.[9–12] Even though similar sized covalent container molecules, constructed from five or six cavitands, have been prepared in multiple steps,[13,14] an approach for their synthesis with efficiencies that are comparable to those of supramolecular approaches remains elusive. Herein, we report the nearly quantitative one-pot synthesis of a nanoscale container molecule by making use of dynamic covalent chemistry.[15,16] In a thermodynamically driven reaction, 18 components condense to form a nanocontainer with an inner cavity of approximately 1700 $Å^3$ that is suitable for encapsulation of biomolecules or multiple organic species. Our approach is not only very efficient stepwise but also atom-efficient, which should facilitate applications of this nanocontainer in medicinal, analytical, chemical, and material sciences.

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[**] This research is supported by the NSF (grants CHE-0431749 and CHE-0518351). We warmly thank Dr. Seho Kim for assistance with PFG-SE NMR experiments.

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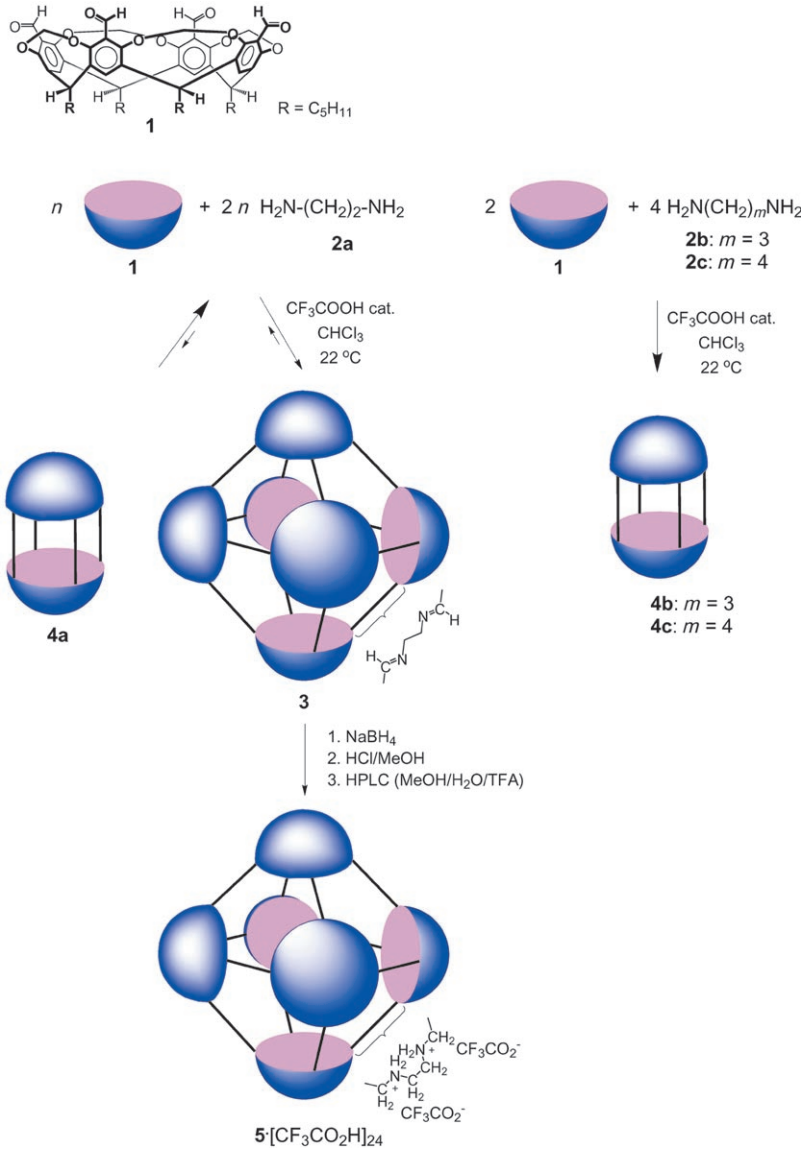
In an investigation of the condensation reaction between the tetraformylcavitand **1** and various diamines, we discovered the spontaneous formation of an octahedral nanocontainer **3** composed of six cavitands that are connected together with 12 diamino bridging units through 24 newly formed imine bonds (Scheme 1). Earlier work showed that the reaction of two equivalents of **1** with four equivalents of 1,3-phenylenediamine is under thermodynamic control and quantitatively yields an octaiminohemicarcerand.[17]



Scheme 1. The thermodynamically controlled condensation of cavitand **1** with diamines **2a–c** leading to nanocontainer **3** or octaiminohemicarcerands **4b** ($m=3$) and **4c** ($m=4$), and reduction of **3** to **5**.

Likewise, the trifluoroacetic acid catalyzed condensation of **1** with 1,3-diaminopropane (**2b**) or 1,4-diaminobutane (**2c**) gave hemicarcerands **4b** and **4c**, respectively, in over 95% yield as supported by NMR and IR spectroscopy, gel permeation chromatography (GPC), and mass spectrometric analysis (Scheme 1). However, when we carried out the same reaction with ethylendiamine (**2a**), the ^{1}H NMR spectrum of the reaction mixture indicated the slow formation of a major product in up to 82% yield with a molecular weight of approximately 6000 Da (GPC; Figure 1a–c). The simplified ^{1}H and ^{13}C NMR spectra are consistent with the octahedrally symmetric **3** being the product of this 18-component condensation reaction (Figure 1c).

The electrospray ionization (ESI) mass spectrum of **3** further supports this conclusion and shows signals for ions $[M+3\,H]^{3+}$, $[M+4\,H]^{4+}$, $[M+5\,H]^{5+}$, and $[M+6\,H]^{6+}$ at m/z 1956.1, 1460.3, 1167.4, and 967.7, respectively. Isolation and purification of **3** proved impossible as a result of the instability of the imine bonds towards normal-phase chromatography. However, after reduction of all the imine bonds of **3** with $NaBH_4$, reversed-phase HPLC purification was possible and nanocontainer **5** was isolated as the trifluoroacetate salt in 63% yield based on **1** (Scheme 1). Again, the ^{1}H and ^{13}C NMR spectra were consistent with the octahedral symmetry of **5**·24 CF_3COOH (Figure 1d).

Furthermore, the ESI mass spectrum of a solution of **5**·24 CF_3COOH in methanol containing 0.1% TFA showed signals at the expected mass-to-charge ratio for ions $[\mathbf{5}+4\,H+n\,CF_3CO_2H]^{4+}$ with $n=0$–8 and for ions $[\mathbf{5}+5\,H+m\,CF_3CO_2H]^{5+}$ with $m=0$–7, which result from the addition of up to 12 CF_3CO_2H units to **5** and the loss of four or five trifluoroacetate anions, respectively, during electrospray ionization. Strong charge repulsions might explain the absence of higher than 12-fold protonated ions, in which at least one linker would be doubly charged.

Unfortunately, crystals suitable for X-ray structure determination could not be obtained. Thus, we probed the size and shape of **3** and **5** by molecular mechanics calculations (Amber* force field; Figure 2).[18,19] From these modeling studies we estimated a cavity volume for **5** of approximately 1700 Å^3, which is large enough to encapsulate multiple guest molecules. That **5** adapts a comparable structure in solution was demonstrated by diffusivity measurements. Pulsed field gradient spin echo (PSG-SE) NMR experiments in CD_3OD containing 0.4% CF_3CO_2D provided a diffusion rate $D=(2.28\pm0.09)\times10^{-6}$ cm^2 s^{-1}.[20] Application of the Stokes–Einstein equation yields a solvodynamic diameter of 3.2 nm, which is consistent with estimates from molecular models.

The vast number of products that the reaction of **1** with **2a** theoretically might lead to and the necessity to correctly form 24 new covalent bonds demands for a greater than 99% yield in each bond-forming step, in order for **3** to be the dominant product of the reaction. Such efficiency in one-pot syntheses of molecular containers is only achievable if an ideal template preorganizes the reactants[21] or, as in this case, if bonds form reversibly, thus allowing for error correction and ultimately furnishing the thermodynamically most stable product.[5,6,8–12,15–17] Our force-field calculations provide some insight into the thermodynamics of this reaction. They show that the spatial arrangement of the cavitands of hypothetical **4a** forces each ethylenediamine unit into a *gauche* conforma-

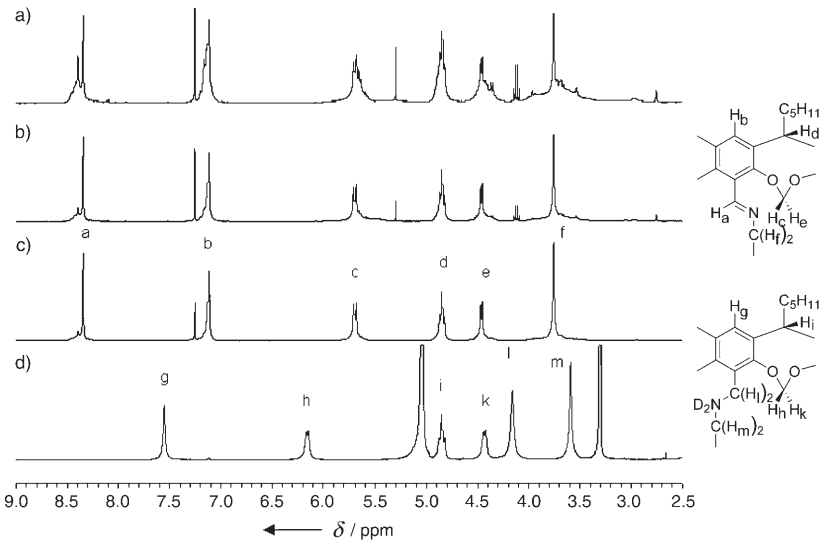


Figure 1. a–c) Partial ^{1}H NMR spectra (400 MHz, 22 °C, $CDCl_3$) of products formed upon mixing **1** with two equivalents of **2a** in $CHCl_3$ containing catalytic amounts of CF_3CO_2H, after a) 0.5 h, b) 3 h, and c) 70 h. d) Partial ^{1}H NMR spectra of **5** (300 MHz, 7 °C, CD_3OD, 0.4 % CF_3CO_2D).

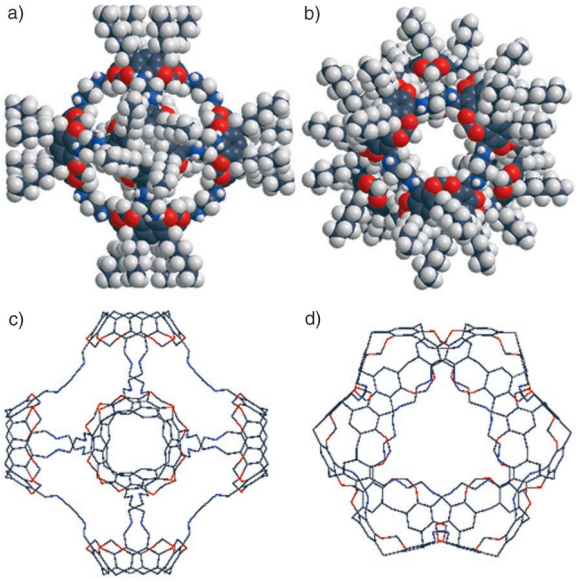


Figure 2. Views along the C_4 (a, c) and C_3 axes (b, d) of energy-minimized structures: a, b) **5**·24 H^+ (space-filling models; Amber* force field,[18] GB/SA water-solvation model[19]); c, d) **3** (stick representation; hydrogen atoms and pentyl groups are omitted; Amber*; vacuum). C gray; H white; O red; N blue.

tion, whereas they are *anti* in **3**, thus minimizing strain within each linker. The fact that condensation of **1** with two equivalents of (*R*,*R*)-1,2-diaminocyclohexane gave polymeric products with molecular weights of greater that 25 000 Da (GPC) rather than the 2:4 hemicarcerand condensation product, which would have been expected based on the preferred conformation of this diamine, suggests that rim-to-rim and/or rim-to-linker interactions might also contribute to the higher stability of **3** versus **4a**. Unfavorable interactions of this kind should increase with decreasing portal size in the host structure, consistent with only the shortest among the investigated diaminoalkanes **2a–c** yielding a hexameric nanocontainer. The fact that nanocontainer **5** is not observed if **1** is treated with two equivalents of **2a** in CH_2ClCH_2Cl or only observed in 17 % yield in $CHCl_2CHCl_2$ shows that the nature of the solvent has a strong influence on the stability of **5** relative to the myriad of other possible oligomeric condensation products. This large solvent effect cannot solely arise from better occupancy of inner space,[22] as part of a solvent molecule can easily protrude through one of the larger openings in the host shell, which have diameters of approximately 8 Å. It suggests that perhaps specific interactions between the solvent and the surface of the host, for which crystallographic studies provide some evidence,[23] are important too and are more favorable for $CHCl_3$ as compared to the other two chlorinated solvents.

We have demonstrated the possibility to synthesize nanosized container molecules from almost 20 components in a single step, which strongly surpasses earlier multistep syntheses in its simplicity and efficiency.[13,14] Our synthesis produces a spherical host that is large enough to encapsulate multiple guests, with portals that should permit polyaromatic compounds easy entrance into its hydrophobic cavity and with functionality that allows derivatization to tailor **5** for specific applications. We see potential uses of **5** and analogues in drug- or pesticide-delivery systems, wastewater detoxification, separation technology, and as molecular reactors for controlled oligomerizations of organic and inorganic monomers. The large variety of reversible bond-forming reactions suitable for dynamic covalent chemistry[15] suggests that other covalent nano-assemblies with spherical or tubular shapes and different properties are accessible through such multicomponent syntheses. The versatility of this approach and the binding properties of **5** are currently being explored in our laboratory.

Experimental Section

Synthesis and characterization of **3** and **5**: A solution of **1**[17] (85.8 mg, 92.3 μmol), ethylene-1,2-diamine (11.1 mg, 184.6 μmol), and CF_3CO_2H (TFA; 0.45 μL, 1 μmol) in $CHCl_3$ (7 mL) was stirred at room temperature under argon for 70 h. A small sample was removed from the reaction mixture, and the solvent was evaporated under high vacuum to yield a yellow solid that contained **3** (82 % by integration of ^{1}H NMR spectra): ^{1}H NMR (400 MHz, $CDCl_3$, 22 °C): $\delta = 8.34$ (s, 24 H; C*H*N), 7.12 (s, 24 H; H_{aryl}), 5.70 (d, ^3J (H,H) = 7.5 Hz, 24 H; $OCH_{out}HO$), 4.83 (t, ^3J (H,H) = 8 Hz, 24 H; $CH(CH_2)_4CH_3$), 4.46 (d, ^3J (H,H) = 7.5 Hz, 24 H; $OCH_{in}HO$), 3.75 (br s, 48 H; NCH_2), 2.25–2.15 (m, 48 H; $CHCH_2(CH_2)_3CH_3$), 1.5–1.3 (m, 144 H; $CHCH_2(CH_2)_3CH_3$), 0.91 ppm (t, ^3J (H,H) = 7.1 Hz, 72 H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 22 °C): $\delta = 157.7$, 153.6, 138.8, 124.5, 121.7, 100.5, 63.2, 36.7, 32.3, 30.1, 27.9, 23.0, 14.4 ppm; IR ($CHCl_3$): $\tilde{\nu} = 2956.8$, 2929.6, 2872.1, 2855.6, 1641.5 (C = N), 1602.6, 1587, 1361.3, 1112.3, 1088.9, 980 cm^{-1}; ESI-MS (CH_2Cl_2/CH_3CN 1:5): *m*/*z* (%): 1954.9 (100) $[M+3H]^{3+}$, 1466.9 (13) $[M+4H]^{4+}$, 1173.7 (3) $[M+5H]^{5+}$.

Nanocontainer **3** was used in the next step without further purification. $NaBH_4$ (150 mg; 4 mmol) and CH_3OH (0.5 mL) were added to a vigorously stirred solution of crude **3** (90 mg) in $CHCl_3$ (7 mL). After 30 min, excess $NaBH_4$ was destroyed by the addition of water (1 mL). The solvent was removed at reduced pressure, and the residue was dissolved in CH_3OH/conc. HCl (10:1). After 3.5 days at room temperature, the solvent was removed. The crude product was purified by reversed-phase HPLC (Vydac RP-18; 10μ; 300 Å; 21 × 250 mm^2; CH_3OH/H_2O/TFA (gradient 85:15:0.1 to 98:2:0.1, 15 min, then hold for 10 min), 15 mL min^{-1}, 280 nm, t_R(**5**) = 13.4 min) to give **5**·24 CF_3COOH as a white solid (84 mg; 63% yield based on **1**): ^{1}H NMR (300 MHz, CD_3OD, 0.4% CF_3COOD, 7°C): δ = 7.55 (s, 24H; H_{aryl}), 6.16 (d, ^3J (H,H) = 6.9 Hz, 24H; $OCH_{out}HO$), 4.85 (t, ^3J (H,H) = 7.6 Hz, 24H; $CH(CH_2)_4CH_3$), 4.43 (d, ^3J (H,H) = 6.9 Hz, 24H; $OCH_{in}HO$), 4.16 (br s, 48H; NCH_2Ar), 3.59 (br s, 48H, $N(CH_2)_2N$), 2.38 (br s, 48H, $CHCH_2(CH_2)_3CH_3$), 1.6–1.2 (m, 144H; $CHCH_2(CH_2)_3CH_3$), 0.92 ppm (t, ^3J (H,H) = 7.1 Hz, 72H; CH_3); ^{13}C NMR (75 MHz, CD_3OD, 0.4% CF_3COOD, 22°C): δ = 160.5 (q, ^2J (C,F) = 37.8 Hz), 155.1, 139.9, 124.6, 119.9, 101.2, 44.4, 42.7, 38.5, 33.1, 30.9, 29.1, 24.0, 14.6 ppm; ESI-MS (CH_3OH/H_2O/TFA 98:2:0.1) *m/z*: 1478.9 $[M+4H]^{4+}$, 1507.3 $[M+4H+TFA]^{4+}$, 1535.5 $[M+4H+2TFA]^{4+}$, 1564.1 $[M+4H+3TFA]^{4+}$, 1592.5 $[M+4H+4TFA]^{4+}$, 1620.7 $[M+4H+5TFA]^{4+}$, 1649.1 $[M+4H+6TFA]^{4+}$, 1677.4 $[M+4H+7TFA]^{4+}$, 1706.0 $[M+4H+8TFA]^{4+}$; elemental analysis (%) calcd for $C_{408}H_{522}F_{72}N_{24}O_{105}$ (**5**·24 CF_3CO_2H·9 H_2O): C 55.62, H 5.97, N 3.82; found C 55.63, H 6.17, N 3.84.

Received: November 15, 2005
Published online: December 30, 2005

Keywords: cavitands · host–guest systems · multicomponent reactions · supramolecular chemistry

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