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A self-assembling metallosupramolecular cage based on cavitand–terpyridine subunits

Tobias Schröder[a], Ralf Brodbeck[a], Matthias C. Letzel[a], Andreas Mix[a], Björn Schnatwinkel[a], Markus Tonigold[b], Dirk Volkmer[b,*], Jochen Mattay[a,*]

[a] Department of Chemistry, Bielefeld University, Universitätsstrasse 25, D-33615 Bielefeld, Germany
[b] Institute of Inorganic Chemistry 2, Materials and Catalysis, Ulm University, Albert-Einstein Allee-11, D-89081 Ulm, Germany

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ABSTRACT

Metal-directed self-assembly of a terpyridyl-functionalized cavitand yields a large hexameric coordination cage.

The formation of supramolecular hollow cages from designed molecular building blocks has fascinated chemists owing to their topological relation to mathematical regular solids (Archimedean solids).[1] Apart from interesting structures, technical applications have been suggested for self-assembled cages including detection and stabilization of encapsulated molecules, the employment as NMR shift reagent, and, more recently, their use as nano-sized reaction vessels that catalyze reactions between encapsulated molecules.[2,3] Pyrogallo[4]arenes and resorcin[4]arenes are valuable building blocks for large supramolecular capsules, as discovered independently and almost simultaneously by Atwood and Mattay.[1a,4] From *upper rim* functionalized cavitands, metallosupramolecular cages built up by up to four units have been obtained.[5] Recently, the X-ray structure of a remarkable one-dimensional polymer containing hexameric cage structures based on a cavitand has been reported.[6] However, the stability of discrete coordination cages in solution yet has to be verified.

Here, we report on the synthesis of a discrete cavitand-based hexameric cage complex by metal-directed self-assembly that is stable in various solvents (e.g., tetrahydrofuran, acetonitrile and acetone). One crucial feature of the cavitand design is four terpyridyl units rigidly attached to the resorcin[4]arene units. While the bowl-shaped cavitand moiety predetermines the optimum geometry for self-assembly into cage structures, the 2,2′:6′,2″-terpyridyl group forms stable complexes with transition metal ions in various oxidation states.[7] The preparation of such tailor-made ligands will be an important strategy to generate large functional cage structures as found in nature in the form of self-assembling multimeric protein cages e.g., ferritin or virus capsides.[8]

The synthesis of the new tetra-(4-(2,2′:6′,2″-terpyridyl)-phenyl)-cavitand **3** was accomplished by Suzuki-coupling of **2** to the tetraiodocavitand **1** (Fig. 1).[9,10]

Initial attempts to prepare a self-assembled spheroidal cage using $Zn(O_3SCF_3)_2$ yielded a product sparingly soluble in acetonitrile. Therefore, the zinc salt $[Zn(NCMe)_6][TFPB]_2$ (**4**) (TFPB = tetrakis-(3,5-bis-(trifluormethyl)-phenyl)-borate) containing lipophilic anions was prepared by a route described for other divalent 3d metal ions.[11–13] Addition of tetrahydrofuran-d_8 to a mixture of 1 equiv **3** and 2 equiv **4** gave the coordination cage **5** after keeping the reaction mixture at 60 °C for 1 h (Fig. 2). The colorless solid is readily soluble in a wide variety of organic solvents, including acetone, tetrahydrofuran, and methylene chloride.

The supramolecular assembly was characterized by ESI-MS, elemental analysis, small angle X-ray scattering (SAXS), and diffusion NMR spectroscopy.

In the ESI-MS spectrum of **5**, multiply charged ions $[\mathbf{5}\text{-}n\ \mathrm{TFPB}]^{n+}$ with $n = 7–11$ were detected at $m/z = 3914, 3317, 2853, 2481$, and

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* Corresponding authors. Tel.: +49 521 106 6920; fax: +49 521 106 6417 (J.M.); tel.: +49 731 502 23921; fax: +49 731 502 23039 (D.V.).

E-mail addresses: dirk.volkmer@uni-ulm.de (D. Volkmer), oc1jm@uni-bielefeld.de (J. Mattay).

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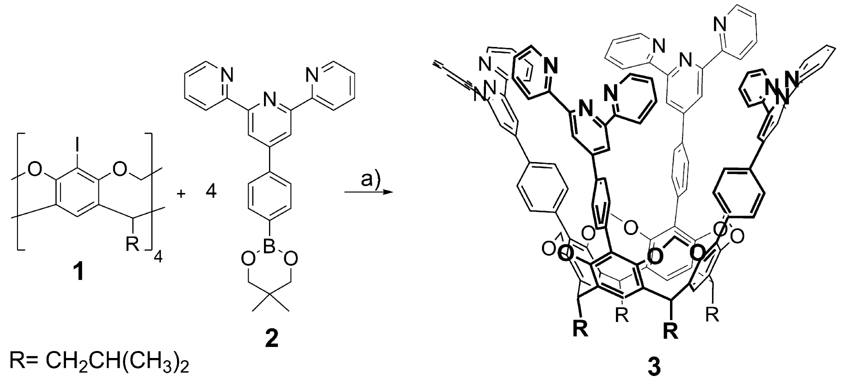

Figure 1. Synthesis of the cavitand **3**: Reagents and conditions (a) [Pd(PPh$_3$)$_4$], Cs$_2$CO$_3$, AsPh$_3$, dioxan/water, reflux, 6 h.

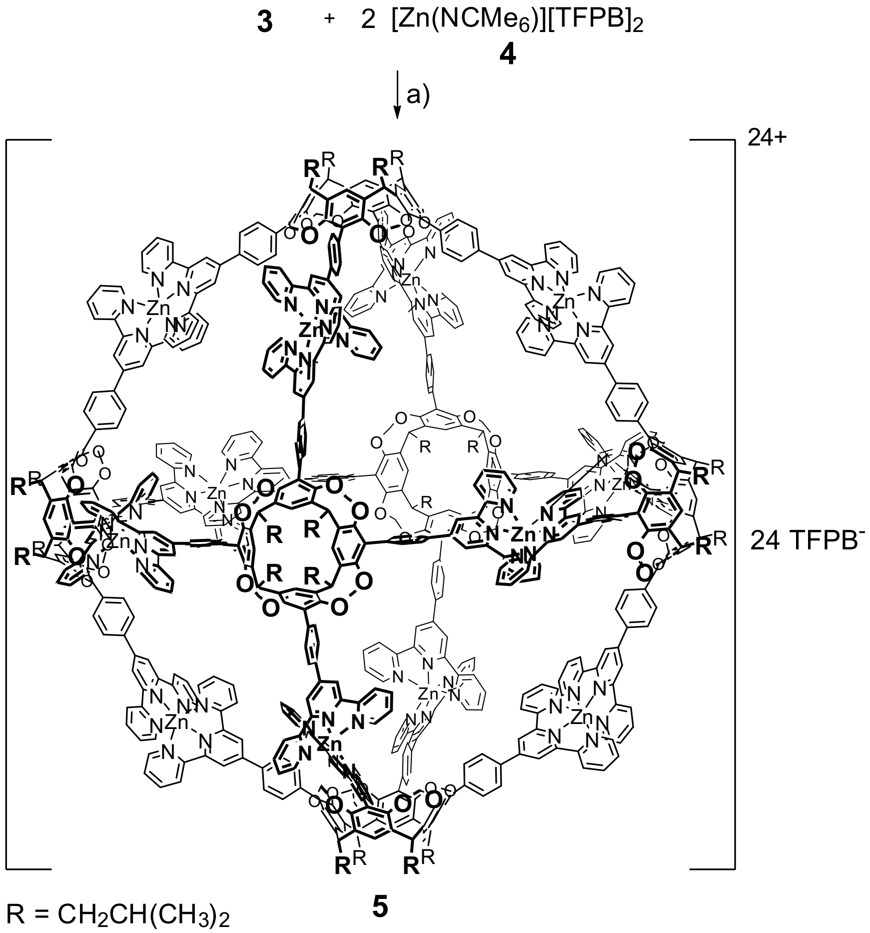

Figure 2. Self-assembly of the supramolecular cage **5** from cavitand **3** and zinc ions. (a) THF-d_8, 60 ° C, 1 h.

2177 containing the intact spheroid cage structure (see Supplementary data). No signals indicating structures of lower aggregation state have been observed.

The ^{1}H-NMR spectrum indicates a high symmetry of the hexameric complex **5**. For all cavitand subunits only one set of signals is observed. The number of signals in the ^{1}H-NMR-spectrum corresponds to average O_h symmetry, since even for the terpyridyl groups only five different signals are detected, which is due to fast rotation of the bis-terpy units resulting in a fast exchange at the NMR timescale at RT. At lower temperatures, the resonances in the aromatic region significantly broaden, but still no distinct signals of the cavitands can be resolved in the aromatic region below −90 °C in acetone-d_6.

Diffusion coefficients D of the cavitand **3** and the coordination cage **5** in tetrahydrofuran-d_8 at 20 °C were $(4.91 \pm 0.04) \times 10^{-10}\ \mathrm{m^2\,s^{-1}}$ and $(2.06 \pm 0.05) \times 10^{-10}\ \mathrm{m^2\,s^{-1}}$, respectively, as determined by diffusion NMR spectroscopy.[14] The diameter of **5** was estimated to be 4 nm,[15] which is in good agreement with the value derived from modeling the cage structure by semiempirical method (PM3) shown in Figure 4.

SAXS measurements, providing the shape and internal structure of particles in solutions,[16] furthermore confirm the formation of

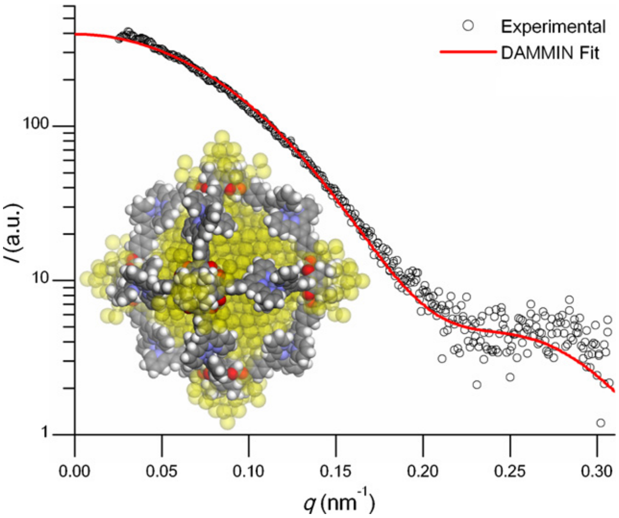

Figure 3. Main plot: SAXS intensity (I) versus momentum transfer ($q = 0{,}2$–$2{,}5\ nm^{-1}$) for a solution of **5** in acetonitrile ($5.1\ g\ L^{-1}$). The symbols and the solid line correspond to the experimental data points and the numerical fit using GNOM/DAMMIN simulated annealing, constraining the symmetry to the point group 432 ($\chi = 1.397$), respectively. Inset: reconstructed low-resolution particle shape for **5** obtained by the GNOM/DAMMIN fit (semitransparent spheres) superimposed to the PM3 stationary point (space-filling model, *iso*-butyl groups substituted by methyl groups).

the supramolecular cage **5**. The logarithmic plot of SAXS intensity (I) versus momentum transfer (q) for **5** is shown in Figure 3, together with the numerical fit to the SAXS data evaluating the shape in solution. The representative reconstruction of the low resolution three-dimensional particle shape was provided by simulated annealing using the GNOM/DAMMIN software packages.[17,18] The obtained radius of gyration (Rg) for **5** of 1.9 nm as well as the reconstructed shape is in good agreement with the expected dimensions of **5**.

Because no crystals suitable for X-ray structure analysis of **5** could be obtained so far, we optimized the structure of the methyl derivate of **5** (R = Me) under the constraint of O symmetry using the semiemperical PM3 method.[19] Figure 4a shows a space-filling representation of the obtained stationary point (assumed to be a minimum).

In the modeled structure of the hexameric assembly, the cavitands are located at the corners of an octahedron, while the zinc ions bridge the organic framework at the edges of the platonic solid.

The cage's dimensions can be illustrated by the distance of approximately 3.9 nm between zinc atoms at opposite edges of the octahedron, or 4.6 nm regarding the largest distance measured between carbon atoms of the methyl groups placed at opposite corners of the modeled structure. The inner cavity of the assembly was evaluated using the program CAVER.[22] The diameter of the largest sphere that fits into the cage structure is approximately 3.0 nm, which corresponds to a volume of about $13.7\ nm^3$. Between the bridging units, openings with a minimal diameter of 0.77 nm exist allowing molecules to enter and to leave the capsule.

Besides solvent molecules, several anions might be enclosed in the positively charged cage structure, although no evidence is found in the NMR spectra. From the volume of the inner cavity, a maximum number of seven tetrakis-(3,5-bis-(trifluormethyl)-phenyl)-borate (TFPB) anions can be estimated to fit inside the cage. Figure 4b shows a representation of the gas phase energy optimized structure of the cage containing seven TFPB anions, as obtained from a force field calculation (see Supplementary data).

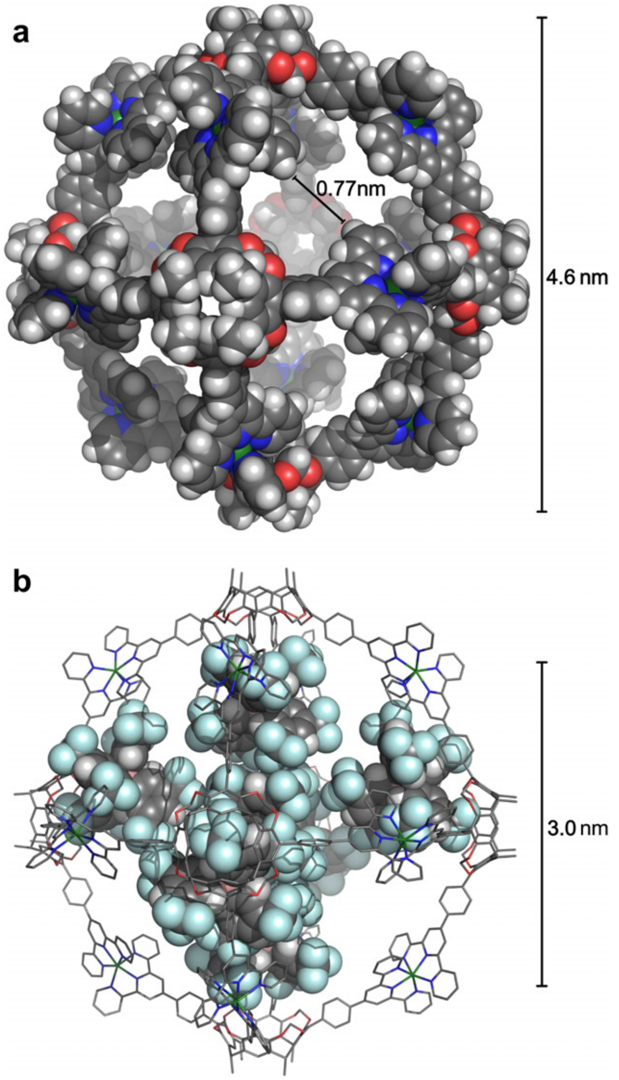

Figure 4. (a) Space-filling representation of the O-symmetric stationary point of the methyl derivate of **5** (R = Me) on the PM3 hypersurface (see Supplementary data for details). (b) Representation of the energy minimized structure of **5** containig seven TFPB anions (*iso*-butyl groups of the cavitands substituted by methyl groups) obtained from a force field calculation.[20,21]

In conclusion, we have demonstrated that large hexameric cage structures can be obtained by metal-directed self-assembly of upper rim terpyridyl-functionalized cavitands. The use of lipophilic anions greatly enhances the solubility of the highly charged assembly in non-polar organic solvents. Studies of its host–guest chemistry are currently pursued in our laboratory. The outstanding complexing properties of the terpyridyl group can afford a wide variety of cage structures by self-assembly of different metal ions in various oxidation states. Since a multitude of functionalized terpyridines are readily accessible, the synthesis of tailor-made terpyridyl cavitands possibly provides highly functional assemblies with extraordinary magnetic, electric, and photophysical properties.

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Supplementary data

Syntheses, experimental methods, ESI-MS spectrum and NMR spectra of **5** and technical details of quantum mechanical and force field calculations. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.143.

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