

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

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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 terpyr-

idyl 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 $\text{Zn}(\text{O}_3\text{SCF}_3)_2$ yielded a product sparingly soluble in acetonitrile. Therefore, the zinc salt $[\text{Zn}(\text{NCMe})_6][\text{TFPB}]_2$ (**4**) (TFPB = tetrakis-(3,5-bis-(trifluoromethyl)-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 $[\mathbf{5}-n \text{TFPB}]^{n+}$ with $n = 7-11$ were detected at $m/z = 3914, 3317, 2853, 2481$, and

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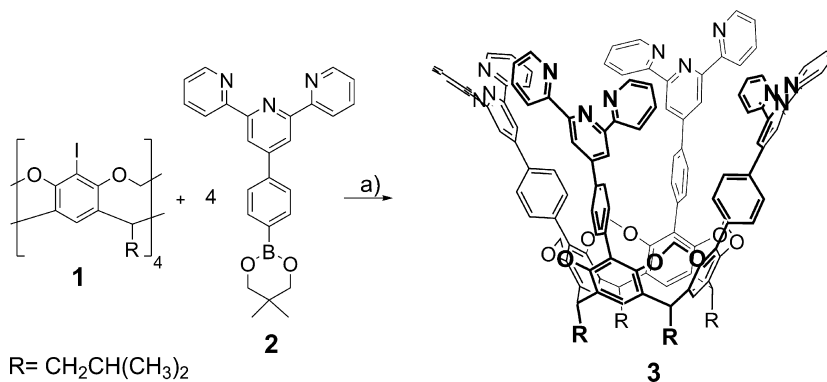


Figure 1. Synthesis of the cavitaand **3**: Reagents and conditions (a) [Pd(PPh₃)₄], Cs₂CO₃, AsPh₃, dioxan/water, reflux, 6 h.

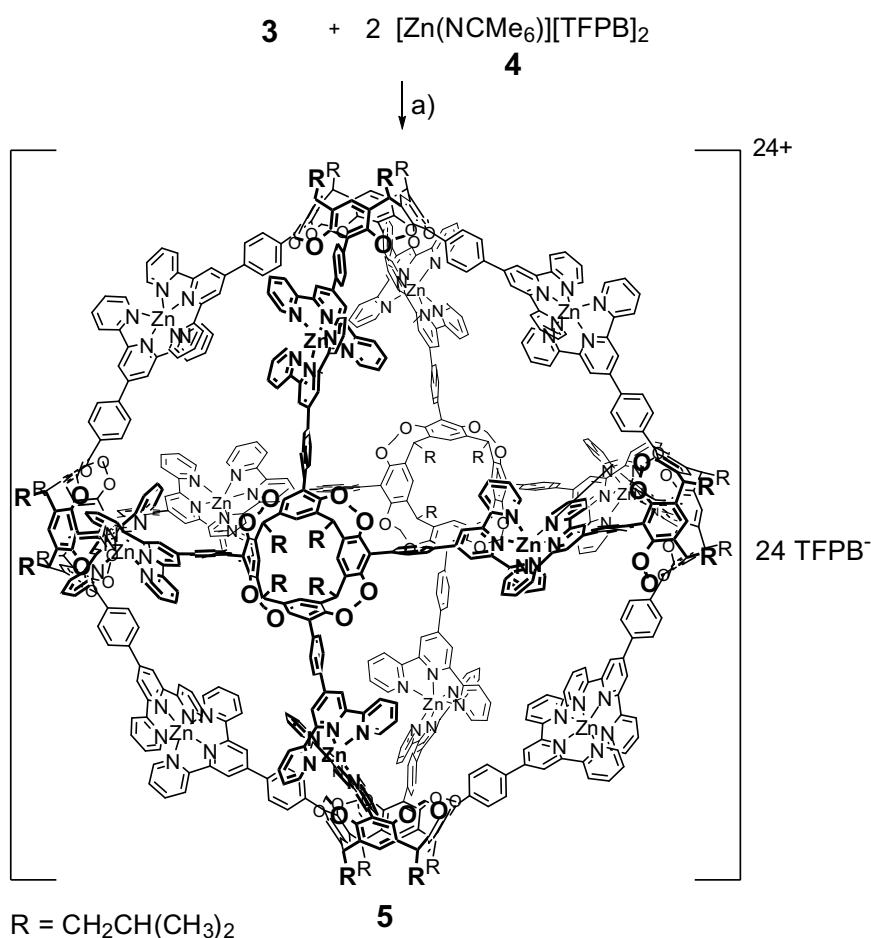


Figure 2. Self-assembly of the supramolecular cage **5** from cavitaand **3** and zinc ions. (a) THF-*d*₈, 60 °C, 1 h.

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

The ¹H-NMR spectrum indicates a high symmetry of the hexameric complex **5**. For all cavitaand subunits only one set of signals is observed. The number of signals in the ¹H-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 sig-

nals of the cavitaands can be resolved in the aromatic region below -90 °C in acetone-*d*₆.

Diffusion coefficients *D* of the cavitaand **3** and the coordination cage **5** in tetrahydrofuran-*d*₈ at 20 °C were $(4.91 \pm 0.04) \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$ and $(2.06 \pm 0.05) \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$, 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

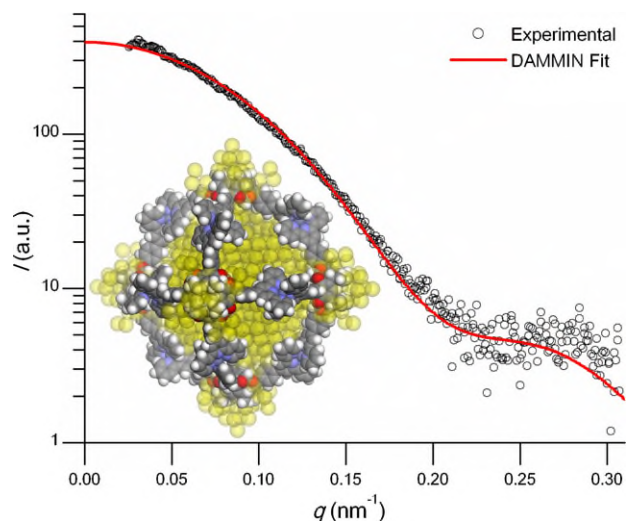


Figure 3. Main plot: SAXS intensity (I) versus momentum transfer ($q=0.2$ – 2.5 nm^{-1}) for a solution of **5** in acetonitrile (5.1 g L^{-1}). The symbols and the solid line correspond to the experimental data points and the numerical fit using $\text{GNOM}/\text{DAMMIN}$ simulated annealing, constraining the symmetry to the point group 432 ($\chi = 1.397$), respectively. Inset: reconstructed low-resolution particle shape for **5** obtained by the $\text{GNOM}/\text{DAMMIN}$ 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 $\text{GNOM}/\text{DAMMIN}$ software packages.^{17,18} The obtained radius of gyration (R_g) 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 derivative of **5** ($R = \text{Me}$) under the constraint of O symmetry using the semiempirical 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-(trifluoromethyl)-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).

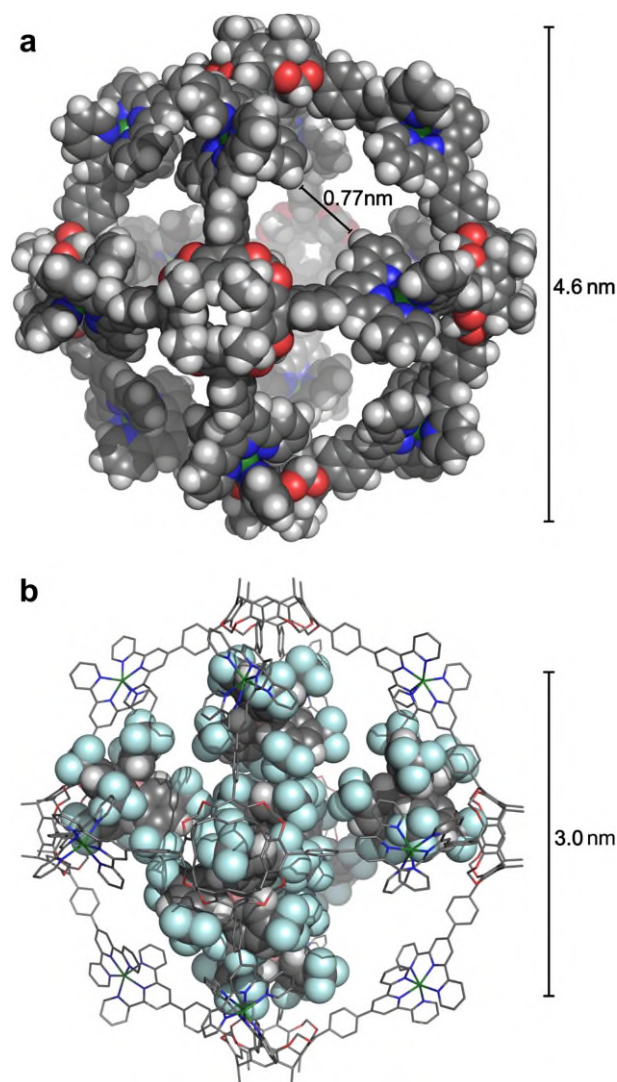


Figure 4. (a) Space-filling representation of the O -symmetric stationary point of the methyl derivative of **5** ($R = \text{Me}$) on the PM3 hypersurface (see Supplementary data for details). (b) Representation of the energy minimized structure of **5** containing seven TFPB anions (*iso*-butyl groups 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.

Acknowledgment

Financial support from the Deutsche Forschungsgemeinschaft (SFB 613, J.M., and SFB 569, D.V.) is gratefully acknowledged. T.S. thanks the University of Bielefeld for financial support. M.T. is grateful for a scholarship of the Graduiertenförderung Baden-Württemberg.

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](https://doi.org/10.1016/j.tetlet.2008.07.143).

References and notes

- (a) McGillivray, R. L.; Atwood, J. L. *Nature* **1997**, *389*, 469; (b) Fujita, M.; Tominaga, M.; Hori, A.; Therrien, B. *Acc. Chem. Res.* **2005**, *38*, 371; (c) Olenyuk, B.; Whiteford, J. A.; Fechtenkötter, A.; Stang, P. J. *Nature* **1999**, *398*, 796; (d) Hof, F.; Craig, S. L.; Nuckolls, C.; Rebek, J., Jr. *Angew. Chem. Int. Ed.* **2002**, *41*, 1488; (e) Müller, I. M.; Möller, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 2969; (f) Oppel, I. M.; Föcker, K. *Angew. Chem., Int. Ed.* **2007**, *13*, 8953.
- (a) Castellano, R. K.; Craig, S. L.; Nuckolls, C.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2000**, *122*, 7876; (b) Kawano, M.; Kobayashi, Y.; Ozeki, T.; Fujita, M. *J. Am. Chem. Soc.* **2006**, *128*, 6558; (c) Ziegler, M.; Brumaghim, J. L.; Raymond, K. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 4119; (d) Körner, S. K.; Tucci, F. C.; Rudkevich, D. M.; Heinz, T.; Rebek, J., Jr. *Chem. Eur. J.* **2000**, *6*, 187; (e) Fox, O. D.; Leung, J. F. Y.; Hunter, J. M.; Dalley, N. K.; Harrison, R. G. *Inorg. Chem.* **2000**, *39*, 783.
- (a) Yoshizawa, M.; Tamura, M.; Fujita, M. *Science* **2006**, *312*, 251; (b) Fiedler, D.; Bergman, R. G.; Raymond, K. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 6916; (c) Kang, J.; Rebek, J., Jr. *Nature* **1997**, *385*, 50; (d) Natarajan, A.; Kaanumalle, L. S.; Jokusch, S.; Gibb, C. L. D.; Gibb, B. C.; Turro, N. J.; Ramamurthy, V. *J. Am. Chem. Soc.* **2007**, *129*, 4132.
- (a) Gerkenmeier, T.; Iwanek, W.; Agena, C.; Fröhlich, R.; Kotila, S.; Näther, C.; Mattay, J. *Eur. J. Org. Chem.* **1999**, 2257; (b) Iwanek, W.; Kotila, R.; Fröhlich, R.; Mattay, J. In: 5th International Summer School on Supramolecular Chemistry (Ustron, Poland) **1996**, Abstract P-31.; (c) Gerkenmeier, T.; Iwanek, W.; Agena, C.; Fröhlich, R.; Näther, C.; Mattay, J. In: 4th International Conference on Calixarenes (Parma, Italy) **1997**, Abstract P-88.; (d) Schnatwinkel, B.; Stoll, I.; Mix, A.; Rekharsky, M. V.; Borovkov, V. V.; Inoue, Y.; Mattay, J. *Chem. Commun.* **2008**. doi:10.1039/b803890b.
- (a) Jacopozzi, P.; Dacanale, E. *Angew. Chem., Int. Ed.* **1997**, *36*, 613; (b) Kobayashi, K.; Yamada, Y.; Yamanka, M.; Sei, Y.; Yamaguchi, K. *J. Am. Chem. Soc.* **2004**, *126*, 13896; (c) Park, S. J.; Hong, J.-I. *Chem. Commun.* **2001**, 1554; (d) Haino, T.; Kobayashi, M.; Chikaraishi, M.; Fukazawa, Y. *Chem. Commun.* **2005**, 2321; (e) Fox, O. D.; Cookson, J.; Wilkinson, E. J. S.; Drew, M. G. B.; MacLean, E. J.; Teat, S. J.; Beer, P. D. *J. Am. Chem. Soc.* **2006**, *128*, 6990.
- Ugono, O.; Moran, J. P.; Holman, K. T. *Chem. Commun.* **2008**, 1404.
- Schubert, U. S.; Hofmeier, H.; Newkome, G. R. In *Modern Terpyridine Chemistry*; VCH: Weinheim, 2006. pp 37–63 and pp 69–124.
- (a) Harrison, P. M.; Arosio, P. *Biochim. Biophys. Acta, Bioenerg.* **1996**, *1275*, 161; (b) Modrow, S.; Falke, D. In *Molekulare Virologie*; Spektrum Akad. Verl.: Heidelberg, 1998. pp. 12–19; (c) Shepherd, C. M.; Borelli, I. A.; Lander, G.; Natarajan, P.; Siddavanahalli, V.; Bajaj, C.; Johnson, J. E.; Brooks, C. L., III; Reddy, V. S. *Nucleic Acid Res.* **2006**, *34*, D386.
- Sebo, L.; Diederich, F.; Gramlich, V. *Helv. Chim. Acta* **2000**, *83*, 93.
- Aspley, C. J.; Williams, J. A. G. *New J. Chem.* **2001**, *25*, 1136.
- Nishida, H.; Takada, N.; Yoshimura, M.; Sonoda, T.; Kobayashi, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2600.
- Brookhart, M.; Grant, B.; Volpe, A. F., Jr. *Organometallics* **1992**, *11*, 3920.
- Buschmann, W. E.; Miller, J. S. *Chem. Eur. J.* **1998**, *4*, 1731.
- (a) Shivanyuk, A.; Rebek, J., Jr. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 7662; (b) Avram, L.; Cohen, Y. *J. Am. Chem. Soc.* **2002**, *124*, 15148; (c) Evan Salem, T.; Baruch, I.; Avram, L.; Cohen, Y.; Palmer, L. C.; Rebek, J., Jr. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 12296; (d) Cohen, Y.; Avram, L.; Frish, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 520; (e) Macchioni, A.; Ciancaleoni, G.; Zuccaccia, C.; Zuccaccia, D. *Chem. Soc. Rev.* **2008**, *37*, 479; (f) Zuccaccia, D.; Pironcini, L.; Pinalli, R.; Dalcanale, E.; Macchioni, A. *J. Am. Chem. Soc.* **2006**, *127*, 7025.
- Zuccaccia, D.; Macchioni, A. *Organometallics* **2005**, *24*, 3476.
- Glatzer, O. *J. Appl. Cryst.* **1979**, *12*, 166.
- Svergun, D. I. *J. Appl. Cryst.* **1991**, *24*, 485; Svergun, D. I. *J. Appl. Cryst.* **1991**, *25*, 495.
- Svergun, D. I. *Biophys. J.* **1999**, *76*, 2879.
- Stewart, J. J. P. *J. Comp. Chem.* **1989**, *10*, 209.
- DeLano, W. L.; Lam, J. W. *PyMOL*; DeLano Scientific LLC: San Francisco (USA), 2006.
- see Supplementary data.
- Petřek, M.; Otyepka, M.; Banáš, P.; Damborsky, J.; CAVER, National Centre for Biomolecular Research, Masaryk University, Masaryk (Czech Republic), **2006**; Damborsky, J.; Petřek, M.; Banáš, P.; Otyepka, M. *Biotechnol. J.* **2007**, *2*, 62; Petřek, M.; Otyepka, M.; Banáš, P.; Košinová, P.; Koča, J.; Damborský, J. *Bioinformatics* **2006**, *7*, 316.