

pH-Responsive Supramolecular Nanovalves Based on Cucurbit[6]uril Pseudorotaxanes**

Sarah Angelos, Ying-Wei Yang, Kaushik Patel, J. Fraser Stoddart,* and Jeffrey I. Zink*

The ability to control the release of molecules from mesoporous silica nanoparticles promises to have far-reaching consequences for drug-delivery applications.^[1] Both molecular and supramolecular nanovalves, which regulate the release of guest molecules from nanopores of mesostructured silica nanoparticles, and operate under a range of stimuli including pH,^[2,3] competitive binding,^[3] light,^[4] and redox control,^[5] have been designed and their successful operation demonstrated^[6] in organic solvents.^[7] These systems are based upon the switching of components that have been tethered to the nanoparticle surfaces, such that access to the entrances of the nanopores can be opened and gated on demand. Since most of the traditional nanovalve designs have been based on [2]pseudorotaxanes^[8] and bistable [2]rotaxanes^[9] that rely upon donor–acceptor and hydrogen-bonding interactions between the ring and stalk components, they are limited largely to use in organic solvents.^[7] However, to realize the potential of nanovalves in therapeutic applications, it is imperative that they not only employ biocompatible components but that they also operate under physiological conditions. For nanovalves to be viable in biological environments, a recognition and binding motif which operates in aqueous media has to be identified, and then tried and tested. Herein, we describe a pH-responsive nanovalve that relies on the ion–dipole interaction between cucurbit[6]uril (CB[6]) and bisammonium stalks, and operates in water.

CB[6], a pumpkin-shaped polymacrocyclic with D_{6h} symmetry consisting of six glycouril units strapped together by pairs of bridging methylene groups between nitrogen atoms,^[10] has received considerable attention because of its highly distinctive range of physical and chemical properties. Of particular interest in the field of supramolecular chemistry

is the ability of CB[6] to form inclusion complexes with a variety of polymethylene derivatives, especially diaminoalkanes: the stabilities of these 1:1 complexes are highly pH-dependent.^[10,11] The pH-dependent complexation/decomplexation behavior of CB[6] with diaminoalkanes has enabled the preparation of dynamic supramolecular entities which can be controlled by pH.^[7,10–13] Another important characteristic of CB[6] is its ability^[12,14] to catalyze 1,3-dipolar cycloadditions,^[15] such that the reaction between an azide-substituted ammonium ion and an alkyne-containing ammonium ion yields a disubstituted 1,2,3-triazole derivative encircled by a CB[6] ring. In view of these particular properties of CB[6], we set about to employ it as a catalyst for the formation of monolayers of [2]pseudorotaxanes on the surfaces of mesoporous silica nanoparticles so as to generate ultimately pH-responsive, biocompatible nanovalves capable of executing different missions.

Mesoporous silica has proven^[1–6,16] to be an excellent support for the formation of dynamic nanosystems, including nanovalves, because it is chemically stable and optically transparent. In this current study, [2]pseudorotaxanes consisting of bisammonium stalks and CB[6] rings were constructed (Figure 1 a,b) on the surface of mesoporous silica nanoparticles, and the pH-dependent binding of CB[6] with the bisammonium stalks is exploited to control the release of guest molecules from the pores of the silica nanoparticles. At neutral and acidic pH values, the CB[6] rings encircle the bisammonium stalks tightly, thereby blocking the nanopores efficiently when employing tethers of suitable lengths. Deprotonation of the stalks upon addition of base results in spontaneous dethreading (Figure 1 b,c) of the CB[6] rings and unblocking of the silica nanopores.

The silica supports employed were approximately 400-nm-diameter spherical particles which contain ordered 2D hexagonal arrays of tubular pores (pore diameters of ca. 2 nm with a lattice spacing of ca. 4 nm) prepared by using a base-catalyzed sol–gel method.^[17] The nanopores were templated by cetyltrimethylammonium bromide (CTAB) surfactants, and tetraethylorthosilicate (TEOS) was used as the silica precursor. Empty nanopores were obtained by removal of the templating agents by solvent extraction. The ordered structure and particle morphology were confirmed (Figure 2) by X-ray diffraction (XRD) and scanning electron microscopy.

This system was designed (Scheme 1 a) such that the nanovalve components could be assembled in a stepwise, divergent manner from the nanoparticle surface outwards. Following solvent extraction, the nanoparticles were heated under reflux in an aminopropyltriethoxysilane (APTES) solution, which afforded the amino-modified nanoparticles 1. These nanoparticles were recovered by vacuum filtration

[*] S. Angelos,^[†] Dr. Y.-W. Yang,^[‡] K. Patel, Prof. J. F. Stoddart, Prof. J. I. Zink
California NanoSystems Institute and
Department of Chemistry and Biochemistry
University of California, Los Angeles
405 Hilgard Avenue, Los Angeles, CA 90095-1569 (USA)
Fax: (+1) 310-206-1843
E-mail: stoddart@chem.ucla.edu
zink@chem.ucla.edu
Homepage: <http://stoddart.chem.ucla.edu>
<http://www.chem.ucla.edu/dept/Faculty/jzink/>

[†] These authors have contributed equally and both should be considered first author.

[**] This research was supported by a Nanoscale Interdisciplinary Research Team (NIRT) grant (ESC-0103559) and a DMR (0346610) grant from the National Science Foundation.

Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

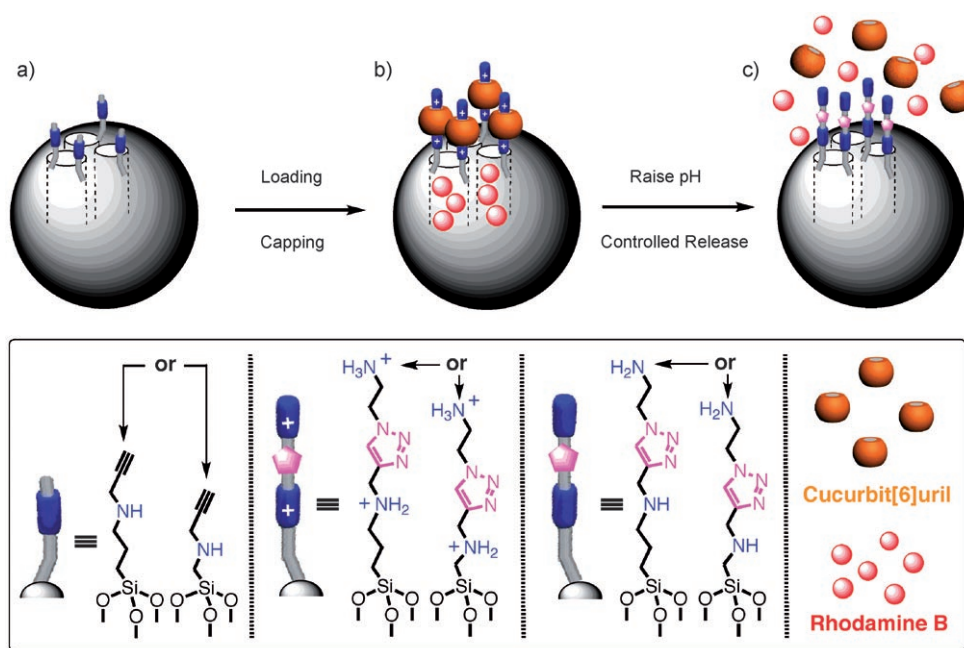


Figure 1. Graphical representations of operating supramolecular nanovalves $\{3\text{C}[\text{CB}[6]]\}$ and $\{6\text{C}[\text{CB}[6]]\}$. The alkyne-functionalized mesoporous silica nanoparticles MCM-41 are loaded (a→b) with rhodamine B (RhB) molecules, and capped (a→b) with CB[6] during the CB[6]-catalyzed alkyne-azide 1,3-dipolar cycloadditions, followed by washing away the excess of substrates. RhB molecules are released (b→c) by switching off the ion–dipole interactions between the CB[6] rings and the bisammonium stalks upon raising the pH value.

before being washed and dried extensively. They were then resuspended in MeOH in the presence of propargyl bromide and heated under reflux overnight to obtain the alkyne-terminated nanoparticles **2**. Next, the empty nanopores in **2** were loaded with fluorescent guest molecules by soaking the nanoparticles in a 0.5 mM solution of rhodamine B (RhB) for 5 h. The preparation of the nanovalves was completed by means of an interfacial CB[6]-catalyzed 1,3-dipolar cycloaddition of the silica-supported alkyne function and 2-azidoethylamine to yield CB[6]/disubstituted 1,2,3-triazole [2]pseudorotaxanes $\{3\text{C}[\text{CB}[6]]\}$ spread all over the silica surface.

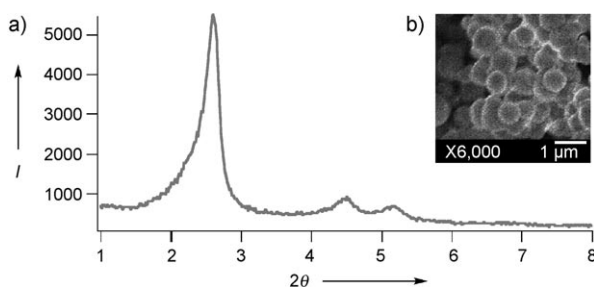


Figure 2. a) The XRD pattern and b) SEM image of the mesoporous silica nanoparticles $\{3\text{C}[\text{CB}[6]]\}$.

The surface functionalization of silica nanoparticles and the construction of the CB[6]-capped nanovalves was monitored by FTIR spectroscopy (see the Supporting Information). The FTIR spectrum of the nanoparticle **2**

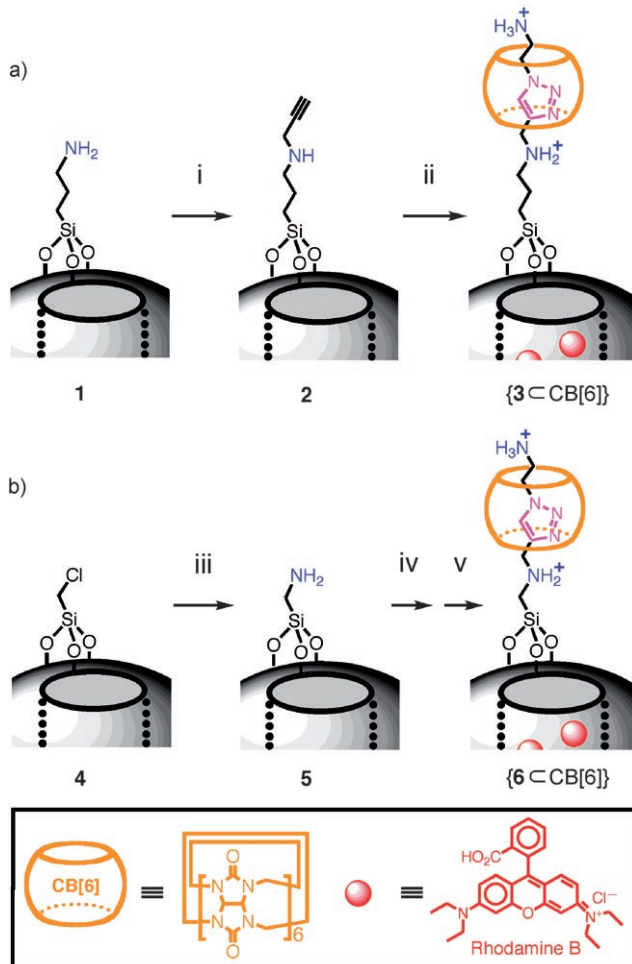
showed new absorption bands at 2131 and 3296 cm^{-1} , which correspond to the alkyne $\text{C}\equiv\text{C}$ and $\text{C}-\text{H}$ stretching modes, respectively. In the FTIR spectrum of the nanoparticles $\{3\text{C}[\text{CB}[6]]\}$, the band at 1632 cm^{-1} corresponding to the CB[6] $\text{C}=\text{O}$ stretching mode confirms the attachment of monolayers of [2]pseudorotaxanes to the surfaces of the silica nanoparticles. The existence of the alkyne $\text{C}\equiv\text{C}$ stretching band at 2131 cm^{-1} infers that not all of the tethered alkyne groups are involved in CB[6]-catalyzed 1,3-cycloadditions, presumably because of the steric hindrance between the [2]pseudorotaxanes congregated on the surface of the silica nanoparticles.

Real-time measurements on the release of RhB have been carried out to monitor

the operation of the nanovalve. Dye-loaded, CB[6]-capped nanoparticles were washed extensively with MeOH and H_2O to remove adsorbed molecules from the surface. A portion of the washed nanoparticles (ca. 15 mg) was placed in the bottom corner of a cuvette, and H_2O (12 mL) was added carefully. A 10 mW, 514 nm probe beam, directed into the water above the nanoparticles, was used to excite the dye molecules as they are released from the nanoparticles. The emission spectrum of RhB was recorded as a function of time at one-second intervals. The nanovalves were opened by adjusting the solution to pH 10 through the addition of 2 M NaOH. Plots of the dissolved dye intensities as a function of time (the release profiles are shown in Figure 3) indicate an increase in the amount of dye released upon base activation, thus demonstrating that the nanovalves do indeed open at high pH values.

In keeping with the development^[6] of prototypical nanovalves, the design of the components usually needs to be optimized to achieve the best possible performance. The situation is no different with the [2]pseudorotaxane $\{3\text{C}[\text{CB}[6]]\}$. The release profile (Figure 3a) reveals that $\{3\text{C}[\text{CB}[6]]\}$ exhibits appreciable leakiness prior to base activation. We suspected that the CB[6] rings in the [2]pseudorotaxanes do not reside close enough to the surface of the mesoporous silica nanoparticles when the nanovalves are closed, thereby making it possible for the RhB molecules to escape prior to base activation. Previous research^[5c] revealed that the critical factors affecting nanovalve activation include 1) the size of the nanovalve components, 2) the positioning of the nanovalves relative to the orifices of the nanopores, and 3) the length of the linker. The outer diameter

of the CB[6] ring^[10] which is 1.4 nm, might be expected to be large enough to gate the approximately 2-nm-diameter pore and thus prevent RhB molecules from escaping. In the synthetic approach summarized in Scheme 1 a, solvent extraction of the sol-gel prior to modification of the silica nanoparticles with amino groups enables the linkers to bind to the pore interiors as well as to the surfaces of the nanoparticles. We suspect, nonetheless, that the bulky CB[6] rings in {3CB[6]} do not penetrate deep enough inside the nanopores, which leaves the nanovalves prone to leakage. Thus, to seal the nanovalves, a shorter linker was employed so that the CB[6] rings would be positioned closer to the surface of the mesoporous silica and so block the nanopore orifices more efficiently. A shorter linker was attached to the silica surface in two steps (Scheme 1 b). The nanoparticles were first of all derivatized with chloromethyltriethoxysilane (CMTES) to afford the nanoparticles **4**, which were then treated with NaNH₂ to produce the amino-modified nanoparticles **5**. The remaining steps of the synthesis of the nanovalve with the shorter linkers were similar to those described earlier (Scheme 1 a) for the nanoparticles with the longer linkers.



Scheme 1. Synthetic route to mesoporous silica nanoparticles functionalized with CB[6]/dialkylammonium pseudorotaxanes. i) and iv) propargyl bromide, MeOH, 50 °C, overnight; ii) and v) 0.5 mM RhB, H₂O, RT, 5 h; then CB[6], 2 N HCl, RT, 3 days; iii) NaNH₂, PhMe, heat under reflux, 12 h.

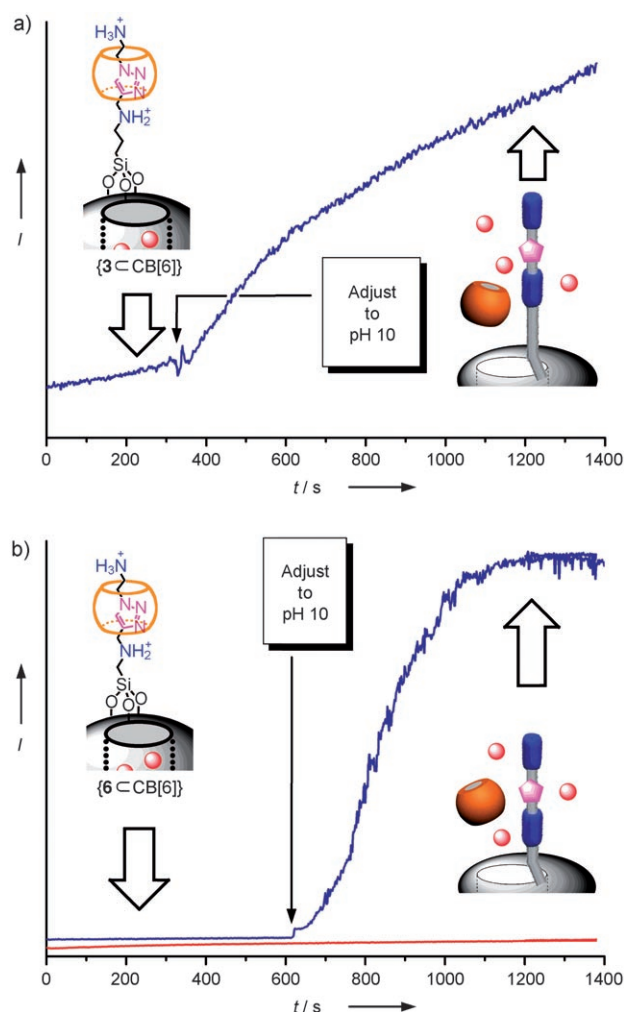


Figure 3. The release of the RhB guest molecules monitored by following the luminescence intensity of the solution of a) nanoparticles with longer linkers {3CB[6]} and b) nanoparticles with shorter linkers {6CB[6]} (blue trace). Control experiments without changing the pH value (red trace) were also performed. Whereas (a) exhibits substantial leakage, as indicated by the premature rise in luminescence intensity, (b) shows no leakage.

The use of the shorter linker curtails the length of the stalk of the pseudorotaxane in {6CB[6]} such that the CB[6] ring is positioned about 0.2 nm closer to the surface of the silica nanoparticle. This subtle change in linker length tightens up the nanovalves sufficiently to prevent leakage, and the release profile illustrated in Figure 3 b is observed.

A concern regarding the operation of these nanovalves is the stability of the silica supports under the high pH conditions required for the nanovalve to function. Activation of the nanovalves relies on deprotonation of the primary alkylammonium and secondary dialkylammonium centers ($pK_a \approx 10$) so as to disrupt the ion-dipole interactions responsible for the binding of the CB[6] rings. To verify that the silica mesostructure and particle morphology are able to withstand the exposure to base (NaOH), which is required for the activation of the nanovalves, scanning electron microscopy (SEM) images and X-ray diffraction patterns of the functionalized nanoparticles were compared (see the

Supporting Information) before and after exposure to base. No noticeable differences in either the nanoparticle morphology or mesostructure were observed, which indicates that the structure of the nanoparticle supports is preserved during the controlled release process.

On reflection, the production of CB[6]-based nanovalves, which employ biocompatible components and operate in water, has been achieved. The nanovalves rely on ion–dipole interactions between the CB[6] rings and the bisammonium stalks attached to the mesoporous silica nanoparticles and can be operated quite simply by raising and lowering the pH value. A modular approach has been developed that relies on the interfacial CB[6]-catalyzed 1,3-cycloaddition of alkyne- and azide-terminated subunits in the final steps of the syntheses of the nanovalves. Now that the validity of exploiting ion–dipole interactions for the design of nanovalves has been established, we anticipate that nanovalves based on CB[6] rings as the gatekeepers will play a significant role in the future of functionalized mesoporous silica nanoparticles for biotechnological and medical applications.^[18] Furthermore, it is conceivable that these pH-responsive supramolecular nanovalves can be tuned to operate under gentler pH stimulation by identifying bisammonium ion centers with pK_a values that will enable the development of CB[6]-based nanovalves for in vivo applications using the natural variations in pH that exist^[19] within healthy and diseased cells in living systems.

Experimental Section

1: Bare mesoporous silica nanoparticles templated by cetyltrimethylammonium bromide (CTAB) were synthesized according to a literature procedure.^[17a] Empty pores were obtained by solvent extraction of the CTAB template: nanoparticles (1.5 g) were suspended in MeOH (160 mL), to which a concentrated aqueous solution of HCl (12 M, 9 mL) had been added, and the mixture was heated under reflux for 24 h. The solvent-extracted nanoparticles were collected by vacuum filtration and washed thoroughly with MeOH. Amino-modification of the silica surface was performed by suspending the nanoparticles (100 mg) in a solution of 3-aminopropyltriethoxysilane (APTES) (1 mM) in dry toluene (10 mL) and heating them under reflux for 24 h. The nanoparticles were collected by filtration, washed thoroughly with toluene, and dried under vacuum.

2: Refluxing aminopropyl-modified MCM-41 nanoparticles **1** in a solution of propargyl bromide in MeOH for 24 h under N_2 (1 atm) afforded the alkyne-modified MCM-41. Extensive washing of the product with MeOH and drying under vacuum resulted in silica nanoparticles **2**. The nanoparticles were characterized by means of FTIR, XRD, SEM, and dynamic light scattering (DLS; see the Supporting Information).

{3CB[6]}: Loading of the pores with rhodamine B (RhB) was carried out by soaking the alkyne-modified porous silica nanoparticles **2** in an aqueous solution of RhB (0.5 mM) for 5 h at RT. A concentrated solution of HCl (12 M, 15 mL) containing an excess of CB[6] and 2-azidoethylamine (see the Supporting Information for the synthesis) was then added to the above mixture. The resulting mixture was stirred for 3 days at RT. The loaded, capped nanoparticles were collected by filtration and washed thoroughly with water to give **{3CB[6]}**, which was characterized by means of FTIR, XRD, and SEM (see the Supporting Information and Figure 2).

5: The bare nanoparticle surface was derivatized with chloromethyltriethoxysilane (CMTES) by adding a suspension of nanoparticles

(100 mg) in CMTES (1 mM) to dry toluene (10 mL) and heating under reflux for 12 h to give the intermediate nanoparticles **4**.^[5c] After adding $NaNH_2$ (0.02 mmol), the reaction mixture was heated at reflux for another 12 h. The aminomethyl-modified nanoparticles **5** were collected by filtration, washed thoroughly with toluene, and dried under vacuum. They were characterized by means of FTIR, XRD, SEM, and DLS.

{6CB[6]}: Nanoparticles **5** were first modified with propargyl bromide by heating under reflux in MeOH under N_2 for 24 h to obtain the alkyne-terminated silica nanoparticles. Loading with RhB and completion of the nanovalve synthesis was achieved as described for nanovalve **{3CB[6]}**. They were characterized by means of FTIR, XRD, and SEM (see the Supporting Information).

Controlled release experiments: The dye-loaded, CB[6]-capped nanoparticles (15 mg) were placed in the corner of a cuvette, and distilled H_2O (12 mL) was added carefully. A 10 mW, 514 nm excitation beam was directed into the solution above the nanoparticles, and the RhB emission spectrum was recorded as a function of time. Release profiles were obtained by plotting the luminescence intensity of RhB at the emission maximum (578 nm) as a function of time. Activation of the nanovalves was accomplished by adjusting the pH value of the solution to 10 by adding 2 M NaOH solution. The solution in the cuvette was stirred gently throughout the controlled release experiment.

Received: November 12, 2007

Published online: February 14, 2008

Keywords: heterogeneous catalysis · host–guest systems · mesoporous materials · molecular devices · surface chemistry

- [1] a) M. Vallet-Regí, A. Rámila, R. P. del Real, J. Pérez-Pariente, *Chem. Mater.* **2001**, *13*, 308–311; b) C. Barbé, J. Bartlett, L. Kong, K. Finnie, H. Q. Lin, M. Larkin, S. Calleja, A. Bush, G. Calleja, *Adv. Mater.* **2004**, *16*, 1959–1966; c) Q. Yang, S. Wang, P. Fan, L. Wang, Y. Di, K. Lin, F.-S. Xiao, *Chem. Mater.* **2005**, *17*, 5999–6003; d) F. Balas, M. Manzano, P. Horcjada, M. Vallet-Regí, *J. Am. Chem. Soc.* **2006**, *128*, 8116–8117; e) M. Arruebo, M. Galán, N. Navascués, C. Téllez, C. Marquina, M. R. Ibarra, J. Santamaría, *Chem. Mater.* **2006**, *18*, 1911–1919; f) S. Angelos, E. Choi, F. Vögtle, L. De Cola, J. I. Zink, *J. Phys. Chem. C* **2007**, *111*, 6589–6592; g) I. I. Slowing, B. G. Trewyn, V. S.-Y. Lin, *J. Am. Chem. Soc.* **2007**, *129*, 8845–8849.
- [2] T. D. Nguyen, K. C.-F. Leung, M. Liong, C. D. Pentecost, J. F. Stoddart, J. I. Zink, *Org. Lett.* **2006**, *8*, 3363–3366.
- [3] K. C.-F. Leung, T. D. Nguyen, J. F. Stoddart, J. I. Zink, *Chem. Mater.* **2006**, *18*, 5919–5928.
- [4] a) N. K. Mal, M. Fujiwara, Y. Tanaka, *Nature* **2003**, *421*, 350–353; b) N. Liu, D. R. Dunphy, P. Atanassov, S. D. Bunge, Z. Chen, G. P. Lopez, T. J. Boyle, C. J. Brinker, *Nano Lett.* **2004**, *4*, 551–554; c) T. D. Nguyen, K. C.-F. Leung, M. Liong, Y. Liu, J. F. Stoddart, J. I. Zink, *Adv. Funct. Mater.* **2007**, *17*, 2101–2110.
- [5] a) R. Hernandez, H.-R. Tseng, J. W. Wong, J. F. Stoddart, J. I. Zink, *J. Am. Chem. Soc.* **2004**, *126*, 3370–3371; b) T. D. Nguyen, H.-R. Tseng, P. C. Celestre, A. H. Flood, Y. Liu, J. F. Stoddart, J. I. Zink, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 10029–10034; c) T. D. Nguyen, Y. Liu, S. Saha, K. C.-F. Leung, J. F. Stoddart, J. I. Zink, *J. Am. Chem. Soc.* **2007**, *129*, 626–634.
- [6] For recent reviews on nanovalves, see a) S. Saha, K. C.-F. Leung, T. D. Nguyen, J. F. Stoddart, J. I. Zink, *Adv. Funct. Mater.* **2007**, *17*, 685–693; b) S. Angelos, E. Johansson, J. F. Stoddart, J. I. Zink, *Adv. Funct. Mater.* **2007**, *17*, 2261–2271.
- [7] The pH-controlled release of guest molecules entrapped in the nanopores of mesoporous silica nanoparticles that have been blocked by surface-grafted, pH-responsive, polyethyleneimine/cyclodextrin poly-pseudorotaxanes has already been described

- in the recent literature; see C. Park, K. Oh, S. C. Lee, C. Kim, *Angew. Chem.* **2007**, *119*, 1477–1479; *Angew. Chem. Int. Ed.* **2007**, *46*, 1455–1457.
- [8] P. R. Ashton, D. Philp, N. Spencer, J. F. Stoddart, *J. Chem. Soc. Chem. Commun.* **1991**, 1677–1679.
- [9] a) J. O. Jeppesen, J. Perkins, J. Becher, J. F. Stoddart, *Angew. Chem.* **2001**, *113*, 1256–1261; *Angew. Chem. Int. Ed.* **2001**, *40*, 1216–1221; b) Y. Liu, A. H. Flood, P. A. Bonvallet, S. A. Vignon, B. H. Northrop, H.-R. Tseng, J. O. Jeppesen, T. J. Huang, B. Brough, M. Baller, S. Magonov, S. D. Solares, W. A. Goddard, C.-M. Ho, J. F. Stoddart, *J. Am. Chem. Soc.* **2005**, *127*, 9745–9759.
- [10] a) J. Lagona, P. Mukhopadhyay, S. Chakrabarti, L. Isaacs, *Angew. Chem.* **2005**, *117*, 4922–4949; *Angew. Chem. Int. Ed.* **2005**, *44*, 4844–4870; b) S. Liu, C. Ruspic, P. Mukhopadhyay, S. Chakrabarti, P. Y. Zavalij, L. Isaacs, *J. Am. Chem. Soc.* **2005**, *127*, 15959–15967; c) J. W. Lee, S. Samal, N. Selvapalam, H.-J. Kim, K. Kim, *Acc. Chem. Res.* **2003**, *36*, 621–630; d) K. Kim, *Chem. Soc. Rev.* **2002**, *31*, 96–107; e) A. Day, A. P. Arnold, R. J. Blanch, B. Snushall, *J. Org. Chem.* **2001**, *66*, 8094–8100; f) W. L. Mock, *Top. Curr. Chem.* **1995**, *175*, 1–24; g) R. Hoffmann, W. Knoche, C. Fenn, H.-J. Buschmann, *J. Chem. Soc. Faraday Trans.* **1994**, *90*, 1507–1511; h) W. A. Freeman, W. L. Mock, N.-Y. Shih, *J. Am. Chem. Soc.* **1981**, *103*, 7367–7368; i) R. Behrend, E. Meyer, F. Rusche, *Justus Liebigs Ann. Chem.* **1905**, 339, 1–37.
- [11] a) C. Marquez, R. R. Hudgins, W. M. Nau, *J. Am. Chem. Soc.* **2004**, *126*, 5806–5816; b) J. W. Lee, K. Kim, K. Kim, *Chem. Commun.* **2001**, 1042–1043; c) D. Tuncel, J. H. G. Steinke, *Chem. Commun.* **2001**, 253–254; d) C. Meschke, H.-J. Buschmann, E. Schollmeyer, *Polymer* **1999**, *40*, 945–949; e) W. L. Mock, J. Pierpont, *J. Chem. Soc. Chem. Commun.* **1990**, 1509–1511.
- [12] a) D. Tuncel, O. Ozsar, H. B. Tiftik, B. Salih, *Chem. Commun.* **2007**, 1369–1371; b) D. Tuncel, J. H. G. Steinke, *Chem. Commun.* **2002**, 496–497; c) T. C. Krasia, J. H. G. Steinke, *Chem. Commun.* **2002**, 22–23; d) D. Tuncel, J. H. G. Steinke, *Chem. Commun.* **1999**, 1509–1510.
- [13] K. Kim, W. S. Jeon, J.-K. Lee, S. Y. Jon, T. Kim, K. Kim, *Angew. Chem.* **2003**, *115*, 2395–2398; *Angew. Chem. Int. Ed.* **2003**, *42*, 2293–2296.
- [14] a) W. L. Mock, T. A. Irra, J. P. Wepsiec, T. L. Manimaran, *J. Org. Chem.* **1983**, *48*, 3619–3620; b) W. L. Mock, A. Irra, J. P. Wepsiec, M. Adhya, *J. Org. Chem.* **1989**, *54*, 5302–5308.
- [15] The Huisgen 1,3-dipolar cycloaddition, in particular the Cu^I-catalyzed stepwise variant, is often referred to simply as the “click reaction”. This “click chemistry” has already been applied successfully in the efficient and convergent template-directed synthesis of mechanically interlocked molecules by our and other research groups; see a) R. Huisgen, G. Szeimies, L. Möbius, *Chem. Ber.* **1967**, *100*, 2494–2507; b) J. Bastide, J. Hamelin, F. Texier, V. Q. Ven, *Bull. Soc. Chim. Fr.* **1973**, 2555–2579; c) W. Lwowski in *1,3-Dipolar Cycloaddition Chemistry, Vol. 1* (Ed. A. Padwa), Wiley, New York, **1984**, chap. 5; d) R. Huisgen, *Pure Appl. Chem.* **1989**, *61*, 613–628; e) H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem.* **2001**, *113*, 2056–2075; *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021; f) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem.* **2002**, *114*, 2708–2711; *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599; g) C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057–3064; h) W. R. Dichtel, O. Š. Miljanić, J. M. Spruell, J. R. Heath, J. F. Stoddart, *J. Am. Chem. Soc.* **2006**, *128*, 10388–10390; i) O. Š. Miljanić, W. R. Dichtel, S. I. Khan, S. Mortezaei, J. R. Heath, J. F. Stoddart, *J. Am. Chem. Soc.* **2007**, *129*, 8236–8246.
- [16] a) P. N. Minoofar, B. S. Dunn, J. I. Zink, *J. Am. Chem. Soc.* **2005**, *127*, 2656–2665; b) E. Johansson, J. I. Zink, *J. Am. Chem. Soc.* **2007**, *129*, 14437–14443.
- [17] a) S. Huh, J. W. Wiench, J.-C. Yoo, M. Pruski, V. S.-Y. Lin, *Chem. Mater.* **2003**, *15*, 4247–4256; b) C. T. Kresge, M. E. Leonowicz, W. J. Roth, J. C. Vartuli, J. S. Beck, *Nature* **1992**, *359*, 710–712.
- [18] a) F. Torney, B. G. Trewyn, V. S.-Y. Lin, K. Wang, *Nat. Nanotechnol.* **2007**, *2*, 295–300; b) J. Lu, M. Liong, J. I. Zink, F. Tamanoi, *Small* **2007**, *3*, 1341–1346; c) B. G. Trewyn, I. I. Slowing, S. Giri, H.-T. Chen, V. S.-Y. Lin, *Acc. Chem. Res.* **2007**, *40*, 846–853.
- [19] a) N. Raghunand, R. Martínez-Zaguilán, S. H. Wright, R. J. Gillies, *Biochem. Pharmacol.* **1999**, *57*, 1047–1058; b) R. Becelli, G. Renzi, R. Morello, F. Altieri, *J. Craniofacial Surg.* **2007**, *18*, 1051–1054.