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A Water-Soluble Deep Cavitand Acts as a Release Trigger for a Supramolecular Nanocap[†]

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Mesoporous silica is widely used as a porous solid support to construct various hybrid materials in catalysis, enzyme immobilization, drug delivery, and imaging.[1] Mesoporous silica nanoparticles are also an attractive carrier for the encapsulation and controlled release of functional molecules for targeted drug delivery. The ordered arrays of nanopores in these particles are of suitable size to contain the desired molecules.[2] The concept of targeted delivery requires that the nanopores be "capped" with the substrate bound inside, and it requires that a mechanical release mechanism be incorporated to allow specificity in delivery. Most examples of this concept use covalent derivatization of the nanopores to introduce a blocking agent.[3] Tetracationic cyclophane-based rotaxane and pseudo-rotaxane caps that can undergo conformational changes triggered by redox chemistry were reported as gatekeepers for mesoporous silica MCM-41.[4] These blocking agents are moved from the pore opening by mechanical switching or fragmentation. Supramolecular association can also be used to control switching processes. For example, supramolecular nanovalves controlled by pH and competitive binding have been developed,[5] and cyclodextrin-based poly(pseudo-rotaxanes) have been reported to control the release of molecules from a mesopore due to pH changes,[6] enzymes, and light.[7] Nanoparticles have also been used to cap/uncap mesoporous silica channels under different stimuli.[8] All these "cap-and-release" methods require covalent derivatization of the mesoporous silica. Another attractive method is to use noncovalent forces to coordinate the cap itself. Derivatized gold nanoparticles (AuNPs) have been used for this procedure, and their binding is dependent on charge: positive nanoparticles have a far greater affinity for the silica than neutral or negative equivalents.[9] Changing the charge profile of the nanoparticles is a mild method of guest release.[9] Here, we discuss a different method that involves the use of targeted supramolecular assemblies to disrupt the nanoparticle: silica association and release the entrapped guest species.

To favor the nanoparticle:silica assembly, alkyl trimethylammonium ligands are attached to the gold nanoparticles. These provide a positive charge to the nanoparticle and are resistant to changes in pH. By introducing water-soluble deep cavitands as host molecules that can selectively bind trimethylammonium groups and interrupt the charge-based interaction between the nanoparticle and silica, guest release is possible. Cavitands are open-ended hosts that bind small molecules of complementary size, shape, and chemical surface.[10] Deep cavitands such as **1** self-assemble to form a cavity whose interior is surrounded by aromatic rings. The electron-rich walls confer an ability to recognize suitably-sized molecules with a thin layer of positive charge on the surface. Tetracarboxylate cavitand **1**[11] shows millimolar water solubility and forms kinetically stable complexes with substituted trimethylammonium cations in water with binding affinities of $> 10^4$ M^{-1}.[12] The strong binding is dominated by

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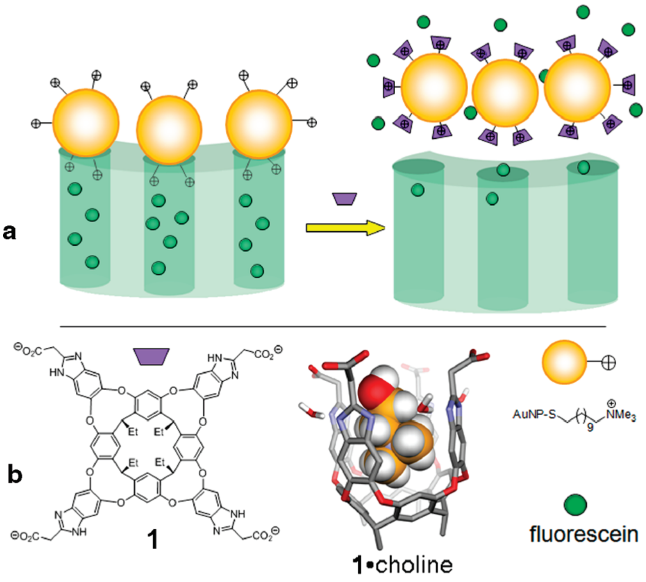

Figure 1. (a) Schematic illustration of the experiment; (b) plan view of cavitand **1** and minimized structure of the 1·choline complex (SPARTAN, AM1).

cation-π interactions between the surface of the guest and the polarized aromatic inner face of the deep cavitand.[13] The positive charge is surrounded by a hydrophobic pocket, effectively shielding this charge from the exterior milieu.

The experiment is shown in Figure 1. The nanopores in mesoporous silica can be filled with guest molecules by simple diffusion, and the pore openings can then be blocked by gold nanoparticles through electrostatic interaction. Upon introduction of cavitand **1**, a strong host: guest interaction will take place, shielding the positively charged trimethylammonium groups, reducing the silica: nanoparticle affinity, and freeing the entrapped guests.

Mesoporous silica MCM-41 was synthesized according to published literature procedures.[8b] The honeycomb-like structure of MCM-41 was confirmed by transmission electron microscopy (TEM) analysis (see Figure 2a). The silica displayed a BET surface area of 973 m^2/g and an average pore diameter of 3.0 nm, as determined by N_2 sorption analysis (see Supporting Information). The positively charged AuNPs were synthesized[14] with a particle diameter of ~8 nm, as determined by TEM analysis (see inset in Figure 2b). The positive charge of the nanoparticle is conferred by attached mercapto-undecyl-trimethylammonium (TMA) ligands; charge measurements show a ζ potential of $+55.1 \pm 3.5$ mV. The aggregation of positively charged AuNPs around negatively charged MCM-41 (ζ potential: -48.5 ± 1.3 mV) can be confirmed by TEM microscopy. Figure 2 shows TEM images of MCM-41 before and after capping with AuNPs.

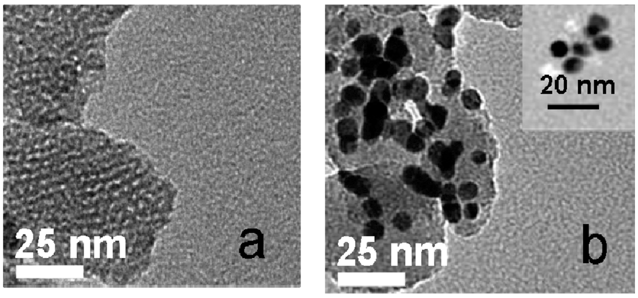

Figure 2. Transmission electron microscopy (TEM) images of (a) MCM-41 and (b) the assembly of MCM-41 with AuNPs. Inset shows AuNPs.

The hexagonally packed mesoporous channels could be clearly visualized before capping. In contrast, the TEM of AuNPs-capped MCM-41 (see Figure 1b) shows dark spots on the exterior surface of the mesoporous silica, representing the aggregation of AuNPs around MCM-41. The presence of AuNPs was also confirmed by the appearance of (111), (200), and (220) diffraction peaks of AuNP in the powder XRD. (See the Supporting Information.)

Cavitand **1** was prepared according to literature procedures.[12b] The vaselike shape of the cavitand is stabilized by an array of hydrogen bonds incorporating water along its upper rim, and one molecule of THF is retained in its hydrophobic cavity during the final synthetic step. When cavitand **1** was added to an aqueous solution of the TMA AuNPs, an assembly was observed. The large molecular mass of the cavitand:nanoparticle conjugate prevents ^{1}H NMR analysis, because of a slow tumbling rate; however, an indirect analysis of the complex formation was possible by monitoring the displaced THF upon nanoparticle addition (see Supporting Information).[12a] The cavitand aggregates with the nanoparticles in solution, with the large aggregate causing significant broadening and disappearance of the signals in the ^{1}H NMR spectrum. THF displaced from the cavity by the trimethylammonium groups is observed in their place, and no precipitation of cavitand from solution is seen.[13] No aggregation was observed when cavitand was exposed to nanoparticles lacking the TMA ligands.

To investigate the ability of this cavitand:AuNP association to control the capping effect of the nanoparticles, fluorescein was loaded into the MCM-41 nanoparticles. MCM-41 was soaked in an aqueous fluorescein solution for 24 h to allow complete saturation. The fluorescein-filled MCM-41 was capped by the addition of the positively charged AuNPs. The excess fluorescein was removed using centrifugation and repeated washing with water and isopropanol. The resulting particles were then dispersed in water, to test their release properties. As shown in Figure 3, without the application of external stimuli, the intensity of fluorescein is essentially constant, indicating no leakage of the entrapped molecules and good efficiency of AuNP to retain entrapped molecules. This system was treated with 0.7 μmol of cavitand **1** in water. Upon the addition of cavitand, the release of fluorescein was observed and quickly reached equilibrium

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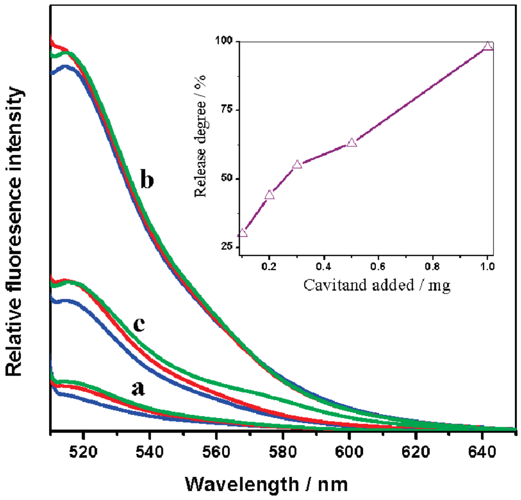

Figure 3. Fluorescence emission spectra of the released fluorescein under (a) no additive, (b) 1 mg (0.73 μmol) of cavitand **1**, and (c) 1 mg (6.94 μmol) of sodium benzoate. (Legend: blue line, 10 min; red line, 30 min; green line, 60 min.) Inset shows the release degree versus the amount of cavitand added.

within 30 min. The final releasing degree and concentration are 99% and 1.98 μM, respectively. The release degree after 30 min of equilibrium time increases as the amount of cavitand added increases (see inset in Figure 3). The result indicates the ability of the cavitand to bind to the TMA groups of the AuNPs, uncap the silica, and allow guest release.

To determine whether this was a truly supramolecular effect, sodium benzoate was used as a control. The tetracarboxylate cavitand could conceivably interfere with the AuNP:silica interaction by nonspecific interactions, because of the charge of the host, rather than a specific noncovalent binding event occurring between the host and TMA groups. Sodium benzoate mimics the charge of the cavitand but lacks any host properties. Upon the addition of an excess of sodium benzoate to the system (Figure 3), a minimal amount of fluorescein leakage was observed (far less than that observed upon cavitand treatment).

The effect of the cavitand:AuNP association is best shown by the change in surface ξ potential of the nanoparticles. The TMA AuNPs have a ζ potential equal to +55.1 ± 3.5 mV. Upon treatment with a cavitand, positively charged NMe^{3+} groups are surrounded by the cavity (a molecular minimization of the structure of **1** binding with choline is shown in Figure 1b). Not only does this "hide" the charge of the headgroups, but it also displays the overall negative charge of the tetracarboxylate cavitand on the nanoparticle surface. The effect of this association reverses the overall charge of the nanoparticle assembly ($\zeta = -47.4 \pm 3.8$ mV), removing the AuNP:MCM-41 interaction. If sodium benzoate is used instead of **1**, the ζ potential is reduced somewhat (ζ potential = +22.5 ± 0.9 mV) but remains positive overall. The large difference can be ascribed to the strong supramolecular interaction between the cavitand and the nanoparticle, which is not observed with sodium benzoate. The reversal of overall charge of the AuNP aggregate allows rapid and facile guest release.

In conclusion, we have described a novel supramolecular nanoswitch based on the specific host–guest interactions of a deep cavitand. The guest molecules trapped inside the nanopore and blocked by gold nanoparticles (AuNPs) can be released in the presence of a cavitand, because of the strong binding of the cavitand with AuNPs and reversal of the AuNP surface charge. No covalent attachments are necessary; the system switches between two host:guest interactions in aqueous solution. The results make the system reported here a promising candidate in the formulation of various responsive nanodevices. This approach could also open new applications of deep cavitands in the construction of molecular nanomachines.

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Supporting Information Available: Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.