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Light-Operated Mechanized Nanoparticles

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As research activity in the field of controlled drug release continues to unfold, many exotic hybrid materials rooted in the use of surfactant templated mesostructured silica,[1] such as MCM-41 nanoparticles (NPs), has become prevalent.[2,3] Several avenues of investigation and development of these materials, including both interior and exterior chemical modification of the frameworks,[4] are being pursued simultaneously. Modification has also led to their subsequent functionalization with a range of different molecular switches that respond to particular stimuli, such as changes in redox potential[5] and pH,[6] as well as the use of enzymes.[7] With drug delivery being one of the potentially most important applications of these mechanized NPs,[5−7] responding to stimuli inside the cell is the most common form of activation. This strategy, however, imposes limitations on the degree of control of designed drug delivery systems and leaves room for undesired activation. An alternative approach involves a system that responds to external stimuli, rather than relying upon internal biological normalities and abnormalities. Light is an external stimulus that can cause a chemical change.[8] Herein, we report (i) the preparation of two azobenzene (AB) derivatives, prepared from 4-(3-triethoxysilylpropylureido)azobenzene (TSUA)[9] and (*E*)-4-((4-(benzylcarbamoyl)phenyl)diazenyl)benzoic acid (BPDB), to give modified MCM-41 NPs; (ii) the effect of probe and excitation beams on light-operated NPs, based on MCM-41 as the cargo container; (iii) the binding and the light-operated dissociation of a pyrene-modified β-cyclodextrin (Py-β-CD) with the TSUA stalks on the surfaces of the MCM-41 NPs, and (iv) the binding of β-CD with the BPDB stalks on the surfaces of the MCM-41 NPs and the light-operated dye (Rhodamine B, RhB) release from the MCM-41 NPs upon dissociation of the β-CD rings from the BPDB stalks.

Irradiating AB with 351 nm light causes AB to isomerize from the more stable *trans* to the less stable *cis* configuration. Previous investigations[10] have demonstrated a high binding affinity in aqueous solution between β-CD and *trans*-AB derivatives and a low, if any, binding between β-CD and *cis*-AB derivatives. In the case of MCM-41 carrying AB-containing stalks, β-CD will thread onto the stalks and bind to *trans*-AB units, thus sealing the nanopores and stopping release of the cargo, e.g., RhB from NPs that have already been loaded with cargo. By contrast, upon irradiation (351 nm), the isomerization of *trans*-to-*cis* AB units leads to the dissociation of β-CD rings from the stalks, thus opening the gates to the nanopores and releasing the cargo. The synthesis and mode of activation of these mechanized NPs are summarized in Figure 1.

MCM-41 NPs (diameters ca. 400 nm) were constituted and functionalized by known procedures.[11] The structures of the NPs were elucidated by X-ray diffraction, and the sizes of the NPs were obtained by dynamic light scattering (see Table S1 in the Supporting Information (SI)). The AB-containing organosilane TSUA was prepared and linked to MCM-41 using the procedures described in the SI. Attachment of TSUA to NPs was confirmed by UV−vis spectroscopy (see Figure S4 in the SI). To increase the surface coverage by the AB-containing stalks but still maintain the hydrophilic character of the NPs, the pseudorotaxanes terminated in their stalks by BPDB units were used for the cargo-release investigation, after being attached efficiently to MCM-41 NPs. The preparation and characterization of the Py-β-CD, a fluorescent host for binding the AB-containing stalks, are described in the SI.

The release of both the Py-β-CD and the RhB cargo from the NPs is monitored by luminescence spectroscopy. A small amount of the solid NPs is placed in the corner of an optical cuvette, and a small stir bar and H_2O are carefully added to avoid disturbing the NPs. A 351 nm excitation beam is directed onto the liquid above the NPs to excite the Py-β-CD and RhB that are released from the NPs into solution under gentle stirring. The maximum amount of cap or cargo that is released is determined by measuring the intensity (excited by the probe beam) after a long period (>400 min) of excitation. A plot of the percent Py-β-CD released as a function of time (the release profile) is shown in Figure 2. Both indirect excitation of the NPs by the probe beam and direct irradiation by the excitation beam cause release, but the latter is much more efficient.

The fluorescence of Py-β-CD is used to measure its dissociation from the mechanized NPs. When the TSUA-derived MCM-41 NPs are added to aqueous solutions containing either β-CD or Py-β-CD, these rings thread onto the stalks and bind to the AB units, forming pseudorotaxanes. When laser light (0.3 W cm^{-2} and 351 nm) is focused on the NPs, the isomerization of *trans*-to-*cis* AB units leads to the dissociation of the rings from the stalks. The release of the Py-β-CD rings can be observed (Figure 2) as an increase in the slope when monitored at 488 nm. Release activated by excitation is much better than that caused by the probe beam. The rate of release was also found to be intermittent when the laser light directed at the NPs was blocked with a beam stop (Figure S8 in the SI). On account of this release dependence on the UV radiation, we investigated further the effect of varying the power of the light source in two independent experiments: they were (i) the irradiation of two different NP samples (from the same stock solution) with different laser powers (Figure S9 in the SI) and (ii) the irradiation of a single sample with increasing power (Figure S10 in the SI). Both experiments revealed increased rates of Py-β-CD

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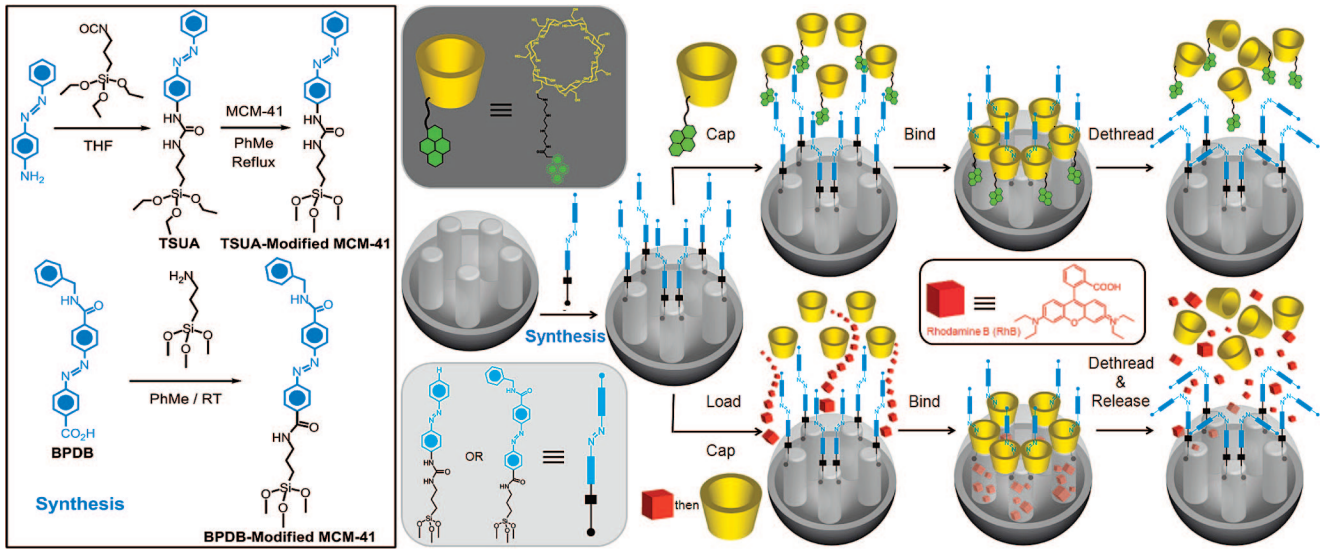

Figure 1. Synthesis of TSUA- and BPDB-modified MCM-41. Two approaches to the operation and function of the AB-modified MCM-41 NPs carrying nanovalves. Py-β-CD or β-CD threads onto the *trans*-AB stalks to seal the nanopores. Upon irradiation (351 nm), the isomerization of *trans*-to-*cis* AB units leads to the dissociation of Py-β-CD or β-CD rings from the stalks, thus opening the gates to the nanopores and releasing the cargo.

release with more powerful UV radiation, thus demonstrating the power dependency of the release very clearly. Also, when a sample of NPs was exposed to a laser light of 0.9 W cm^{-2} at 647 nm, where AB units do not absorb, there was no change in its release profile when compared with a sample that was not exposed to any laser light other than the probe beam. These observations indicate that localized heating is not an explanation for the release observed from NPs irradiated at 351 nm and 0.3 W cm^{-2}. We also considered the possibility that the observed release profiles might be a result of photodecomposition of the TSUA-derived stalks. Such an occurrence would mean that we are observing a photolabile blocking mechanism rather than the proposed association/dissociation mechanism controlled by the stereochemistry of the AB units. To rule out the former mechanism, two samples of the TSUA-derived NPs were examined as follows: one was exposed to 0.3 W cm^{-2} of UV light (351 nm) for more than 1 h, and the other (a control) was left unexposed. The UV−vis spectra of the two samples were identical and displayed no release of the AB fragments into solution, indicating that there is no degradation of the TSUA-derived stalks under the experimental conditions (Figure S11 in the SI).

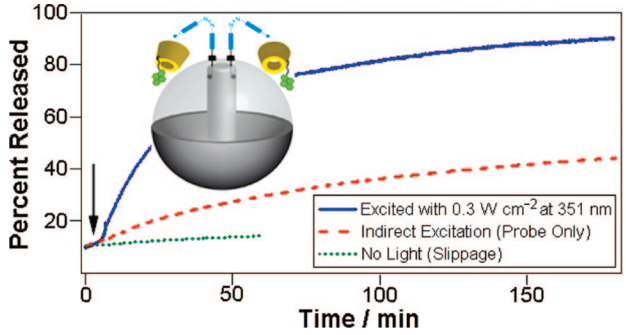

Figure 2. Release profiles for Py-β-CD as a function of time when monitored at 488 nm. The bottom trace (green dots) reflects the amount of Py-β-CD lost to solution as a result of nonlight activated slippage of the Py-β-CD. The slope of this trace is close to zero meaning the association between the AB stalks and the Py-β-CD is stable when left unexposed to UV radiation (351 nm). The middle trace (red dashes) is from a sample that is constantly exposed to a probe beam (0.4 W cm^{-2}, 377 nm). The slope of this line increases slightly as the system is very sensitive to UV light and is activated by the probe beam to a small degree. The top trace (blue line) reflects the release of Py-β-CD when the NPs are exposed to the excitation beam. These traces indicate that the system is stable in the dark, very sensitive to UV radiation, and can release the majority of the associated Py-β-CD when exposed to a large number of UV-photons. Note that 100% release is determined by allowing the loaded NPs to be exposed to radiation over 400 min total.

Next, we sought to demonstrate that β-CD rings can prevent dye molecules (RhB) from leaving the MCM-41 nanopores while they are associated with the AB *trans* units in stalks and are then released once the CD rings are dissociated as a consequence of the light-promoted isomerization of *trans*-to-*cis* AB units. However, when the TSUA-derived NPs were modified to increase the surface coverage and reduce leakage of the dye, the NPs became too hydrophobic to load with RhB. Thus, we employed the more water-soluble BPDB-derived stalks on the NPs. Two identical samples of RhB-loaded and β-CD ring-associated BPDB-derived NPs were prepared. One sample was exposed for 7 h to laser light (351 nm), while the other (a control) was left unexposed. The results show (Figure 3a) that >90% of RhB is released from the exposed sample whereas <30% is released from the unexposed one. These results indicate that, upon irradiation, the isomerization of *trans*-to-*cis* AB units leads to the dissociation of the β-CD rings from the stalks, thus opening the gates of the nanopores and hence permitting the release of the cargo. An experiment was also performed to monitor the simultaneous release of both Py-β-CD and RhB from the same sample. The results show (Figure 3b) a direct correlation between the release of the Py-β-CD rings and RhB molecules into solution, indicating that the rings are directly responsible for constraining RhB molecules within the nanopores.

In conclusion, we have designed and made light-operated mechanized NPs that are able to retain dye molecules and then release them upon exposure to light. The operation is based on the association and light-operated dissociation of the β-CD and/

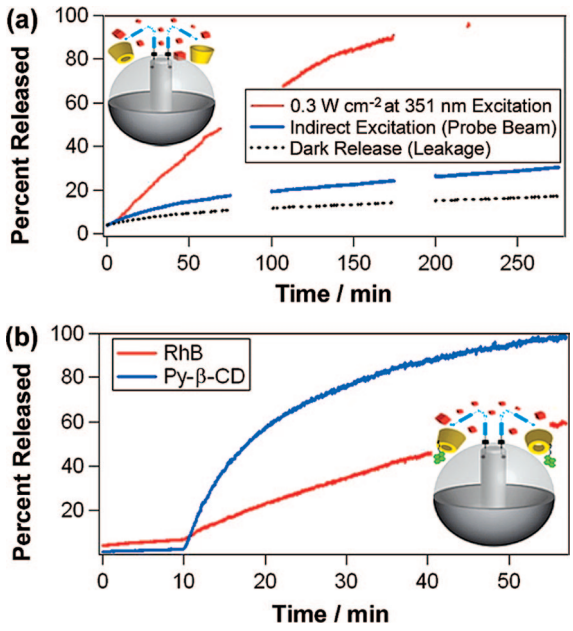

Figure 3. (a) Upon UV irradiation (red line) of the RhB loaded and β-CD-associated NPs, >90% of RhB is released over 150 min; when the RhB-loaded NPs were exposed only to the probe beam (blue line), <30% of RhB is released during 150 min; when the probe laser is pulsed (black dotted line) the leakage of RhB is observed. (b) An increase in the release rates of the Py-β-CD rings and the RhB upon UV irradiation (at 10 min) occurs, demonstrating the relationship between the release of the Py-β-CD rings and RhB into solution.

or Py-β-CD rings with the AB-containing stalks on the surfaces of the MCM-41 NPs. External control could help us localize and optimize the process of drug delivery. The hydrophilic character of the mechanized NPs and their ability to release stored drug molecules in response to an external light source make this system applicable to light-operated intracellular drug delivery systems.

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

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