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Multiresponsive Supramolecular Nanogated Ensembles

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Supramolecular chemistry has been widely used in the construction of molecular shuttles, molecular motors, and nanomachines.[1] Because of the unique features of mesoporous silica (MS), such as uniform and tunable pore structure, and great diversity in surface functionalization, MS has been employed as a useful and versatile solid support for constructing various hybrid materials in catalysis, enzyme immobilization, drug delivery, and imaging.[2]

By combining functional supramolecular parts, a series of MS-based supramolecular nanovalves for controlled release have been developed that are responsive to distinct external stimuli. Tetracationic cyclophane-based rotaxane and pseudorotaxane caps that could undergo conformational changes triggered by redox chemistry were first reported as gatekeepers for mesoporous silica MCM-41.[3] Supramolecular nanovalves that could be controlled by pH and competitive binding were later developed.[4] Cyclodextrin (CD), a well-known and readily available molecular host in supramolecular chemistry, has recently been used as a new functional component for building up MS-based stimuli-responsive nanocarriers. CD-based polypseudorotaxanes could work as pH-responsive molecular gates to control the release of molecules from a mesopore due to its pH-dependent capability of threading/dethreading the ethyleneimine polymer grafted on MCM-41.[5] Alternative methods for MS-controlled release using enzyme[6] and light[7] have also been studied using CD-based rotaxane and pseudorotaxane, respectively.

Responsive polymers are another widely used functional component for constructing MS-based controlled release systems, such as thermoresponsive nanocontainers from poly(NIPAAM)-MS hybrid materials.[8] We recently introduced cross-linkable polymer into mesoporous silica to construct a redox-responsive nanogated system, in which a labile polymeric network could work as a gatekeeper to control the transport of molecules.[9] In this work, we seek to develop a multiresponsive nanogated system by integrating the advantages of a polymeric network as capping agent with the versatile assembly/disassembly of CD-based supramolecular chemistry. Herein we report a novel supramolecular nanogated material responsive to different stimuli relying on distinct motifs. The system is based on MS grafted with β-CD-bearing polymer (denoted as poly-CD-MS). The working principle is illustrated in Figure 1. The polymer around the silica can be cross-linked to form a polymeric network to block molecule transport by the addition of diazo-linker, a water-soluble ditopic guest molecule with an azobenzene group at each end.[10] Such cross-linking is possible because it is well established that the *trans*-azobenzene group has a high binding affinity with β-CD. On the other hand, such a binding complex dissociates when *trans*-azobenzene is transformed to *cis*-azobenzene upon photoirradiation.[7,11] Therefore, the polymeric network that blocks the pore of MS can be opened by cleaving the linkage with UV irradiation, leading to light-controlled release (pathway a).

The dissociation of supramolecular complex and the release of entrapped molecules can also be realized by addition of competitive host α-CD, which favors the formation of inclusion complexes with an azobenzene group more than β-CD does[10,11b,12] (pathway b). Furthermore, since β-CD is linked to the polymer main chains through the S−S bond, the polymeric network can also be opened by cleaving the disulfide bond in the presence of disulfide reducing agents such as dithiothreitol (DTT), leading to the redox-controlled release (pathway c).

Poly(*N*-acryloxysuccinimide)-grafted mesoporous silica (denoted as PNAS-MS) was obtained by using a previously reported method.[9] Substitution of the *N*-oxysuccinimide group along the polymer with *S*-(2-aminoethyl)thio-2-thiopyridine gave an intermediate material (denoted as poly-Py-MS) with pyridyldithio functionality, which was confirmed by the characteristic peaks of acrylamide at 1650 cm^{-1} and pyridine ring at 1450 cm^{-1} in FTIR spectra (Figure S1, Supporting Information). Since the pyridyldithio functionality is widely used for efficient thiol-coupling,[13] β-CD was easily immobilized onto the polymer via the S−S linkages by thiol-coupling reaction between pyridyldithio group and per-6-thio-β-cyclodextrin[14] in dimethylformamide (DMF) to give the desired hybrid material, poly-CD-MS.

X-ray diffraction and N_2 sorption measurements showed that the hybrid materials retain the mesoporous structure upon functionalization with β-CD (Figure S2, SI). The relative IR peak intensity of pyridine ring in poly-CD-MS decreased, while several new characteristic peaks from per-6-thio-β-cyclodextrin were observed after β-CD immobilization (Figure S1), which confirmed the successful substitution of pyridyldithio groups by β-CD through S−S bonds. Pyridinethione, released from the thiol-coupling reaction, exhibited a strong absorption at ~370 nm (Figure S3, SI), and the amount of pyridinethione released was estimated to be 1.17 mmol/g poly-Py-MS by using the reported molar extinction coefficient (5800 M^{-1} cm^{-1}) of pyridinethione in DMF.[13b] Thermogravimetric analysis (TGA) showed 6% more weight loss for poly-CD-MS (61% weight loss) than for poly-Py-MS (55% weight loss), resulting from the weight difference of conjugated β-CD and the released pyridinethione. From the amount of pyridinethione released and the difference between TGA weight losses, the concentration of β-CD in the hybrid materials is about 0.196 mmol/g poly-CD-MS.

To investigate the multiresponsive gating behavior of the hybrid nanomaterials, calcein was loaded as model molecule by soaking poly-CD-MS in a phosphate-buffered saline (PBS) solution (pH 7.4) of calcein. An appropriate amount of diazo-linker (1:2 molar ratio of diazo-linker and β-CD in Poly-CD-MS) was then added into the mixture to cross-link the polymer chains around MS. The excess calcein was removed by centrifugation and repeated washing with PBS buffer. The loading of calcein was determined to be 0.080 mmol/g hybrid materials. The calcein-loaded particles were then dispersed in the PBS buffer to test their controlled release property. As shown in Figure 2 (curve a), without the application of external stimuli, no release was observed, indicating no leakage of the entrapped molecules and good efficiency of the supramolecular network to retain entrapped molecules. When UV light (0.3W cm^{-2} and 365 nm) was focused on the releasing solution, the release of calcein was observed due to the

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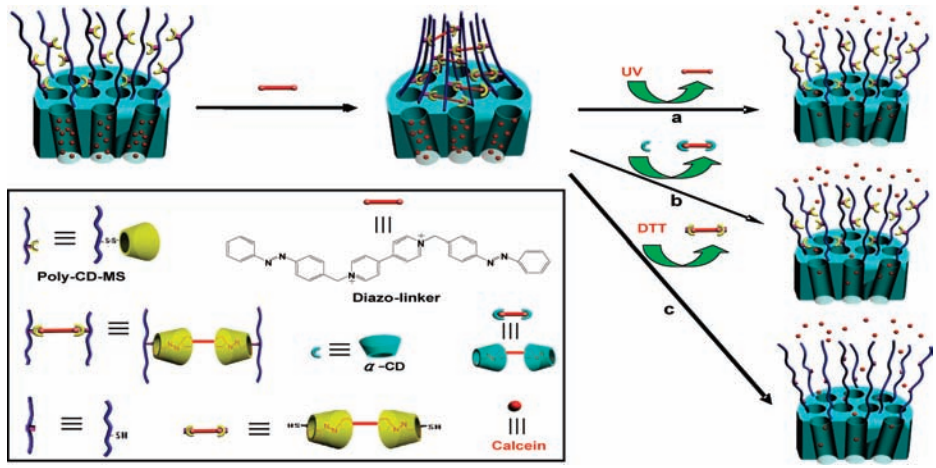

Figure 1. Schematic illustration of a multiresponsive nanogated ensemble based on supramolecular polymeric network-capped mesoporous silica.

dissociation of cross-linked polymer complex resulting from the *trans*-to-*cis* isomerization of the azobenzene group under UV light (Figure 2, curve b). The release reached about 30% equilibrium at 30 min, which is consistent with the reported 30 min required for the *trans*/*cis* photostationary state.[15] The lower releasing saturation amount under UV irradiation may be ascribed to the existence of some *cis*-azo/β-CD complex and hence the partially stable cross-linked network. The addition of DTT also induced the release of entrapped molecules, and the release profile (Figure 2, curve c) exhibited faster releasing dynamics than that under UV light. The presence of excess α-CD induced molecule transport at a much faster rate, with saturated releasing concentration at 0.0056 mM relative to that of DTT, which is believed to be the result of higher solubility[16] and association complex constants[12] of α-CD relative to thiolated β-CD released through the S−S breaking. Such different releasing behavior under the different conditions can be used to meet the desirable nanogating requirements.

In conclusion, we report here the controlled release of molecules from mesoporous silica particles by using a supramolecular polymer network as a multiresponsive valve. Poly-CD-MS was filled with model molecules and then blocked by adding diazo-linker to cross-link the β-CD-bearing polymer chains around the outer surface of mesoporous silica. The trapped molecules were released from the hybrid materials by the cleavage of the polymeric network using UV irradiation, competitive binding, or the addition of a disulfide reducing agents, dithiothreitol. The multiresponsive supramolecular nanogating hybrid materials exhibit distinct releasing properties under different external stimuli, which makes the system reported here promising to meet the various requirements in biosensor and *in vivo* site-specific drug delivery applications.

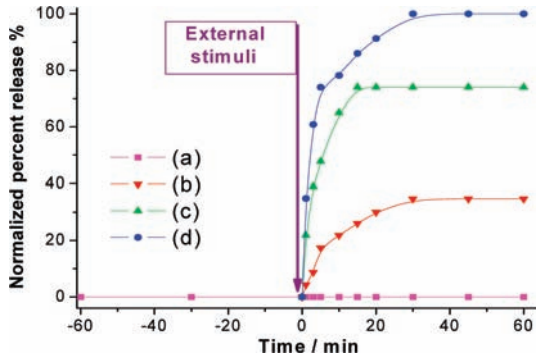

Figure 2. Controlled release of calcein from cross-linked poly-CD-MS (1.0 mg) in 1 mL of PBS solution (100.0 mM, pH 7.4). (a) No noticeable release was observed without external stimuli. At time 0, triggered by (b) UV, (c) 5 mg of DTT (after 60 min, 5 mg more DTT did not induce more release), (d) 5 mg of α-CD (~30 equiv to β-CD of poly-CD-MS, after 60 min; 5 mg more α-CD did not induce more release).

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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.

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