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Tunable Redox-Responsive Hybrid Nanogated Ensembles

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Materials that can trap and release molecules controllably hold promise for sensor and drug delivery applications.[1] The great diversity in surface functionalization of mesoporous silica together with their uniform and tunable pore size and high surface area bestows such materials with unique advantages in the construction of nanocontainers that are responsive to stimulus. Different nanomaterials have been achieved. For example, CdS and Fe_3O_4 nanoparticles have been used as the capping agent to control opening/closing of pore entrance of mesostructured materials.[2] A photocontrolled release system based on coumarin functionalized mesoporous materials was demonstrated.[3] Polyamines anchored on the pore outlets of mesoporous materials as a dual pH- and anion-driven gate-like ensemble have also been demonstrated.[4] A series of supramolecular nanovalves using redox,[5a−c] pH,[5d,e] competitive binding,[5f] light,[5g] and enzyme[5h] as actuators have also been demonstrated.

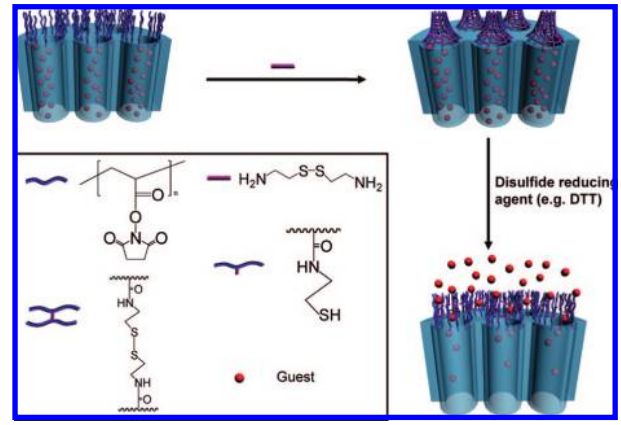
Polymeric micelles, another type of functional nanomaterials, have been extensively studied for their applications as delivery vehicles, molecular imaging agents, and microelectronic devices.[6] Recent progresses in this area are mainly focused on core or shell cross-linked polymeric micelles, where the cross-linked layers work as a barrier to modulate molecular transport as well as a stabilizer to improve the micellar integrity.[7] However, these types of organic carrier-based systems suffer from inherent low stability in a biochemical environment or in organic solvents used for drug loading. Integration of both polymeric organic and inorganic components into a functional system represents a unique advantage.

Here for the first time, a cross-linked polymeric network is used as a "gatekeeper" on the surface of mesoporous silica-based materials. The gate operation is based on redox reactions in which the cross-linked polymeric network works as an off−on switch in response to redox signals.

The system consists of poly(*N*-acryloxysuccinimide)-grafted mesoporous silica (denoted as PNAS-MS), in which the polymers are attached at the pore entrance of MCM-41 particles. The working principle of the system is illustrated in Scheme 1. After loading the dye molecules into porous silica particles, the openings of PNAS-MS are blocked by the addition of cystamine, a disulfide-based bifunctional primary amine, which allows polymer chains to be cross-linked through the reaction between cystamine and *N*-oxysuccimide groups along the polymer chain. The polymeric network thus formed around the pore opening can be reopened by cleaving the disulfide bond of cystamine in the presence of disulfide reducing agents such as dithiothreitol (DTT), leading to the redox-controlled release.

Poly(*N*-acryloxysuccinimide) was anchored to the outlet of silica mesopore through reversible addition-fragmentation chain transfer (RAFT) polymerization (see detailed synthesis pathway and procedure in the Supporting Information). RAFT polymerization has emerged as a promising living radical polymerization method in functionalization of a solid surface because of its versatility and compatibility with almost all of the conventional radical polymerization monomers. The absence of metal catalyst in RAFT makes it better suited for the bioapplication than ATRP. The successful grafting of polymer onto mesoporous silica was confirmed by the appearance of a band at 1730−1822 cm^{-1}, which is characteristic of ester carbonyl and two cyclic carbonyl group of NAS, in the FTIR spectroscopy (Figure S1). TEM (Figure 1) showed that PNAS-MS retained the pore structure as the parent MCM-41 and a uniform 2 nm thick polymer coating was observed around the silica particle after grafting. Thermogravimetric analysis (TGA) of the hybrid materials yielded 58% weight loss from the grafted polymer when heated in the N_2 atmosphere to 800 °C while almost no weigh loss was observed for pure MCM-41 in the same temperature range (Figure S2).

Scheme 1. Schematic Illustration of Redox−Responsive Nanogated Ensemble Based on Polymeric Network-Capped Mesoporous Silica



Poly(*N*-acryloxysuccinimide) around the entrance of mesopore can be cross-linked by adding cystamine.[7e,8] The successful cross-linking of NAS units of PNAS-MS was confirmed by various spectroscopic methods. A decrease in intensity of powder X-ray diffraction (XRD) peaks may be ascribed to the pore-filling effect induced by cross-linking (Figure S3).[2] N_2 sorption measurement of PNAS-MS exhibited the typical type IV isotherms of mesoporous materials while cross-linked PNAS-MS showed an isotherm characteristic of nonporous materials (Figure S4). The change of

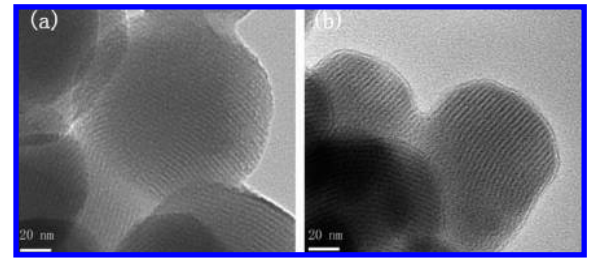


Figure 1. TEM of (a) MCM-41 and (b) PNAS-MS.

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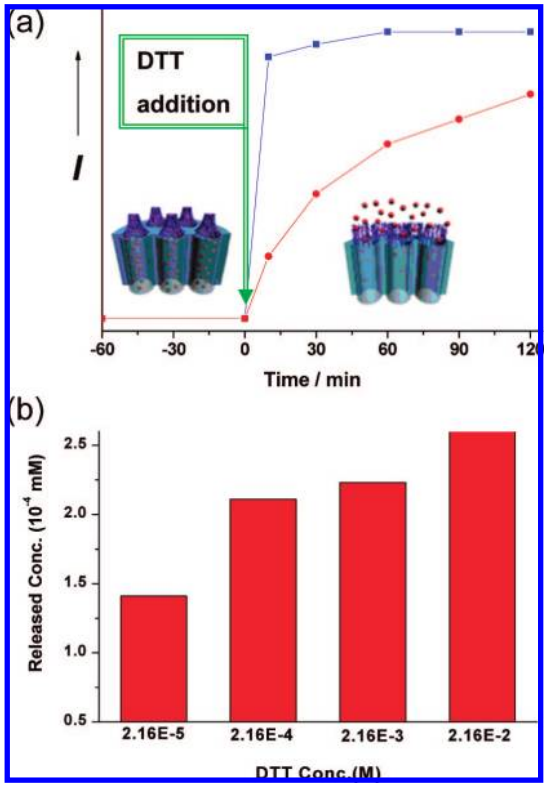

Figure 2. (a) Time course of rhodamine B release from hybrid materials in the presence of DTT concentrations 2.16×10^{-2} M (blue) and 2.16×10^{-4} M (red). (b) The DTT concentration-dependent releases. Released dye concentrations are measured after 2 h of the DTT addition.

sorption type together with a decrease of surface area and pore size distribution indicated the capping effect of the polymeric network after cross-linking.[2] The FTIR peaks (Figure S1) around 1730−1822 cm^{-1} disappeared while the absorption peaks of amide groups at around 1558−1651 cm^{-1} appeared,[9] which further confirmed the substitution of *N*-oxysuccimide unit by cystamine. TGA of cross-linked PNSA-MS showed 51% weight loss (Figure S2), the lower weight loss compared with PNAS-MS indicated the substitution of *N*-oxysuccimide with cystamine in the molar ratio 2:1 between *N*-oxysuccimide and cystamine, the optimal reaction ratio to form the cross-linked network.[10]

To investigate the redox-responsive gating behavior of the hybrid nanomaterials, rhodamine B was first loaded by soaking PNAS-MS in a phosphate-buffered saline (PBS) solution (pH 7.4) of rhodamine B. Then, cystamine was added into the mixture to cross-link the polymer chain around the outlet of mesoporous silica. The excessive rhodamine B was removed by centrifugation and repeated washing with water. The resulting particles were then dispersed in the PBS buffer to test their controlled release property. Prior to the addition of DTT, the intensity of rhodamine B is essentially constant, indicating no leakage of the entrapped dye molecules. The addition of DTT induced the release of dye molecules, and the release profile in Figure 2a exhibited a rapid molecular transport in the presence of a high concentration of DTT (2.16×10^{-2} M). In comparison, the dye delivery is relatively slow at a low DTT concentration (2.16×10^{-4} M), indicating the gate-like ensemble is ajar. The effect of DTT concentration can be further confirmed in Figure 2b as the released dye concentration is positively dependent on the added DTT amount. This behavior can be ascribed to the different degrees of cleavage due to the difference in the concentration of the disulfide reducing agent, which demonstrates the tunable gating effect of the material reported here. In comparison, 1,6-hexadiamine cross-linked ensemble shows no induced release with the addition of DTT.

In conclusion, we report here the controlled release of guest molecules from mesoporous silica particles by using polymer network as a redox-responsive valve. PNAS-MS was filled with guest molecules and then blocked by adding cystamine to cross-link the PNAS chain around the pore opening. The loaded molecules were released from the hybrid materials by the cleavage of the disulfide linker of the polymeric network with the addition of disulfide reducing agents dithiothreitol (DTT). Since disulfide bonds can also be cleaved by using cell-produced antioxidants (e.g., dihydrolipoic acid or glutathione), the system reported here is promising for biosensor and in vivo site-specific drug delivery. This approach could also provide a general route to graft other functional polymers onto the surface of silica particles for various applications.

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Supporting Information Available: Experimental details, characterization data for MCM-41, PNAS-MS, and cross-linked PNAS-MS. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) See TGA calculation in the Supporting Information.

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