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pH-Responsive Nanogated Ensemble Based on Gold-Capped Mesoporous Silica through an Acid-Labile Acetal Linker

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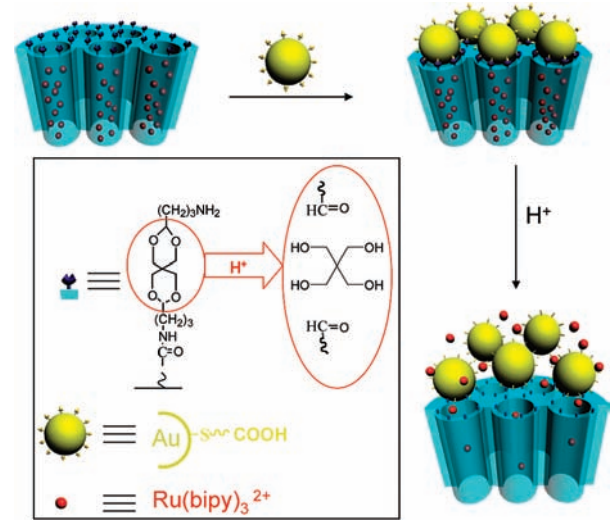
Due to their high surface area, uniform and tunable pore structure, and diversity in surface functionalization, mesoporous silica (MS) has been widely used as versatile solid supports to construct hybrid materials for catalysis, enzyme immobilization, drug delivery, and imaging.[1] A series of MS based controlled release systems have been developed that are responsive to distinct external stimuli. For example, a photocontrolled release system based on coumarin functionalized mesoporous materials has been demonstrated,[2] and dual pH- and anion-driven gated ensembles using polyamines anchored on the pore outlets have also been reported.[3] A series of supramolecular nanovalves using redox,[4a−c] pH,[4d−f] competitive binding,[4g] light,[4h,i] and enzyme[4j] as actuators have also been demonstrated, and we recently reported cross-linkable polymer modified mesoporous silica as a new type of versatile responsive system.[5] Nanoparticles have also been widely used as capping agents in MS release systems. CdS and Fe_3O_4 nanoparticles were first used to control the opening and closing of the pore entrance of mesostructured materials through redox-dependent S−S bond cleavage.[6] Recently, gold nanoparticles were used as blocking caps to control the transport of cargo from mesoporous silica through either a reversible pH-dependent boronate ester bond[7a] or photo-controlled electrostatic interaction.[7b]

Acid sensitive drug delivery vehicles are highly desired in the treatment of acidic targets, such as tumors and inflammatory tissues. Several acid degradable linkers have been used in the construction of prodrug conjugates, lipids, polymeric micelles, and nanogels to deliver therapeutic contents in acidic pH environments. For example, hydrazone or *cis*-aconityl linkers have been reported in the construction of polymer−doxorubicin (DOX) conjugates to control the release of the attached anticancer drug DOX in a physiological and acidic environment.[8] pH-sensitive polyethylene glycol (PEG) lipids containing an orthoester linkage demonstrated their pH-dependent degradation and showed potential use in gene delivery.[9] Polymeric micelles with anticancer drug adriamycin (ARD) attached to the core via an hydrazone bond are stable at physiological pH but degrade and release ARD at lower pH.[10] The protein-loaded hydrogels or microgel based on acetal cross-linkers release encapsulated protein at pH 5.0 while the release is inhibited at pH 7.4.[11] Here, we introduce an acid cleavable linker into an MS-based controlled release system and report a new pH-responsive nanogated ensemble by capping the gold nanoparticle onto the mesoporous silica through an acid-labile acetal linker. As shown in Scheme 1, at neutral pH, the linker remains intact and pores are blocked with gold nanoparticles to strongly inhibit the molecular diffusion from the pores. At acidic pH's, the hydrolysis of the acetal group will remove the gold cap and allow escape of the entrapped molecules in a pH-dependent controlled release.

Scheme 1. Schematic Illustration of pH-Responsive Nanogated Ensemble Based on Gold-Capped Mesoporous Silica through Acid-Labile Acetal Linker



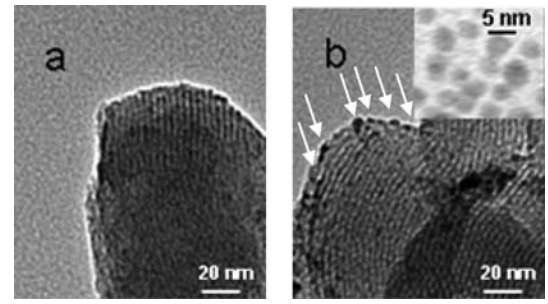


Figure 1. TEM of (a) MS-Acetal, (b) MS-Au, and, in inset in (b), Au-COOH

To create this nanogated ensemble, carboxylic acid groups were first introduced onto the outlet of mesoporous silica (denoted as MS-COOH) using an established method.[4f] Then, the acetal containing linker was grafted on by the reaction of excess 3,9-bis(3-aminopropyl)-2,4,8,10-tetraoxaspiro[5.5]undecane with the carboxylic acid modified MS, followed by the removal of the surfactant template by acetone extraction[12] to produce MS-Acetal. The TEM in Figure 1a, XRD in Figure S1a, and N_2 sorption measurement in Figure S2 demonstrate a typical hexagonal mesopore channel for MS-Acetal. A fluorescamine test (Figure S3) confirmed the presence of free amine from the attached acetal linker whereas no amine was detected on MS-COOH. The free amine groups were then coupled with COOH groups on the carboxylic acid modified gold nanoparticle (Au-COOH[13]) to cap the gold nanoparticles onto the mesoporous silica (MS-Au). The successful capping was confirmed by various spectroscopic methods. Powder

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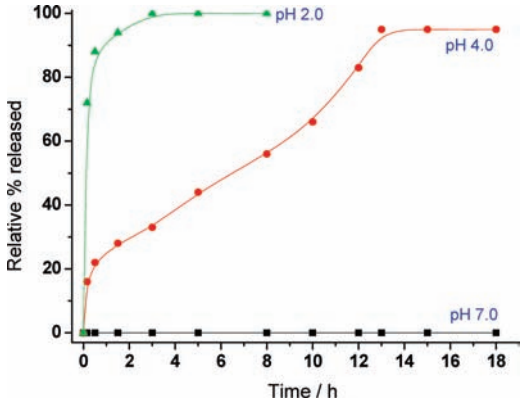

Figure 2. Time course of dye release from MS-Au at different pH's.

X-ray diffraction (XRD) (Figure S1a) in $2° < 2\theta < 8°$ showed that MS-Au remained mesoporous despite the lower intensity of XRD peaks that may be ascribed to the pore-filling effect induced by gold nanoparticle capping.[6] XRD in the $30° < 2\theta < 70°$ range (Figure S1b) showed similar (111), (200), and (220) diffraction peaks to those observed for Au-COOH, supporting the presence of gold nanoparticles on MS-Au. N_2 sorption measurement of MS-Acetal exhibited the typical type IV isotherms of mesoporous materials while MS-Au showed an isotherm characteristic of nonporous materials (Figure S2). The change of sorption type, together with a decrease of surface area and pore size distribution, is expected due to the capping effect of the nanoparticles.[6] TEM showed that Au nanoparticles are clearly visible as dark spots on the outside of the mesopores (indicated in the Figure 1 by arrows) while characteristic mesoporous channels remain. The large decrease in the amount of free amino for MS-Au in the fluorescamine test (Figure S3) demonstrates that Au nanoparticles are indeed coupled through amide bonds.

To investigate the pH-responsive gating behavior of the hybrid nanomaterials, $[Ru(bipy)_3]Cl_2$ (bipy = 2,2′-bipyridine) dye was loaded as a guest by soaking MS-Acetal in an aqueous solution (pH 7.0) of $[Ru(bipy)_3]Cl_2$. Then, Au-COOH was added into the mixture to cap the mesoporous silica in the presence of EDC/NHS (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide/*N*-hydroxysuccinimide). The excessive dye was removed by centrifugation and repeated washing with water. The resulting particles were then dispersed in water at different pH's to test their controlled release property. At pH 7.0, no free dye was observed, indicating an efficient capping of the agent. The pH 4.0 solution, however, induced the release of dye molecules with the profile shown in Figure 2 that reaches 100% release at 13 h. At pH 2.0, faster molecular transport was observed with 90% release in 30 min and equilibrium in 2 h with the final concentration 0.0014 mM. The effect of pH upon the release tracks the degradation rates of acetal groups at different pH's. It has been reported that while the acetal linker is stable from pH 6−8.2, it is completely hydrolyzed in 30 min at pH 2.0 and in 12 h at pH 4.0.[14] The release profile at different pH's herein matches well with the reported degradation profile of the acetal group. Two additional control studies were carried out. In the first, we used MS-Acetal as a nanocontainer to trap the dye molecules without further capping by the gold nanoparticle. In the second, we used already capped MS-Au to adsorb the dye molecules mainly at the external surface. After the same washing procedure, no molecule release was observed at any pH because the absorbed molecules escaped from unguarded pores or an external surface during the washing steps, which again confirms the previously observed release due to dye molecules trapped within the pH-responsive gold-capped nanogated vessel.

In conclusion, we report here the controlled release of guest molecules from mesoporous silica particles by using acid-labile acetal group linked gold nanoparticles as pH-responsive capping agents. The guest molecules were blocked from the hybrid materials at neutral pH and released at lower pH. The release profile is strongly dependent on the cleavage of the acetal linker at different pH's. The results make the system reported here a promising candidate in the formulation of a pH-sensitive vehicle for in vivo delivery of therapeutic agents to low pH tissues, such as tumors and inflammatory sites. This approach could also provide a general route to graft other sensitive linkers onto the surface of silica particles for a wide range of applications.

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

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