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Dual-Controlled Nanoparticles Exhibiting AND Logic

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Molecule-based logic systems and their potential applications are receiving increasing attention.[1,2] Logic gates are binary switches whose input conditions (0 or 1) determine the output state (0 or 1). Most of the chemical systems that are capable of performing simple logic operations employ small molecules or biomolecules as inputs and a fluorescence signal as the output.[1−3] In the research reported here, we present dual-controlled nanoparticles (DCNPs), in which two different types of machines, namely, nanoimpellers[4] and nanovalves,[5] are brought together in and around mesoporous silica nanoparticle supports (Figure 1). The molecular machines are designed to operate in tandem with one another in such a way that the DCNP systems function as AND logic gates and provide sophisticated control of the contents of the pores.

Recently developed mesoporous silica nanoparticles functionalized with supramolecular as well as molecular machines have shown promise as drug-delivery vehicles, since guest molecules, such as small organic molecules and drug molecules, can be stored within the nanopores of the mesoporous silica while the surface-mounted machines can be operated by external stimuli to control their release.[6,7] On-command release systems responding to a range of stimuli, including light,[7a−f] pH,[7g−i] competitive binding,[7j] enzymes,[7k] and redox activation,[7l,n] have been reported by us and others. In the DCNP systems discussed here, light-responsive nanoimpellers[4,7c] and pH-responsive nanovalves[7g,h] are operated in tandem with one another in such a way that the release of encapsulated guest molecules (the output) requires activation of *both* the nanoimpellers using 448 nm light (input 1) and the nanovalves using pH changes (input 2). Two different pH-responsive nanovalve systems have been employed in this work, resulting in the formation of two different DCNPs: DCNP-**1**, which employs base-responsive nanovalves, and DCNP-**2**, which features acid-responsive nanovalves.

While both nanoimpellers and nanovalves function independently as controlled-release mechanisms, they are based on entirely different principles and activated by different types of stimuli. Nanoimpellers are based[4,7c] on photoresponsive azobenzene derivatives that are tethered[8,9] to the inner pore walls of the mesoporous silica nanoparticle supports. Azobenzene exists in two configurations (trans and cis) and can be interconverted between the two upon absorption of light. When azobenzene derivatives attached to the nanopore interiors are exposed to a wavelength of light that is absorbed by both the trans and cis isomers, a dynamic wagging motion,[9] which can be used to impel unbound guest molecules out of the nanopores, is generated within these derivatives. On the other hand, the nanovalves employed here are based[10,11] on pH-switchable [2]pseudorotaxanes in which cucurbit[6]uril (CB[6]) rings encircle bisammonium stalks that are tethered to the outer surfaces of the nanoparticle supports. The base-responsive nanovalves used in DCNP-**1** consist of CB[6]/bisalkylammonium [2]pseudorotaxanes. At neutral pH, the bulky CB[6] rings interact tightly with the tethered stalks through ion-dipole interactions, blocking the nanopore orifices and trapping the guest molecules. When the pH is increased and the stalks become deprotonated, the binding interactions are disrupted, and the CB[6] rings dissociate from

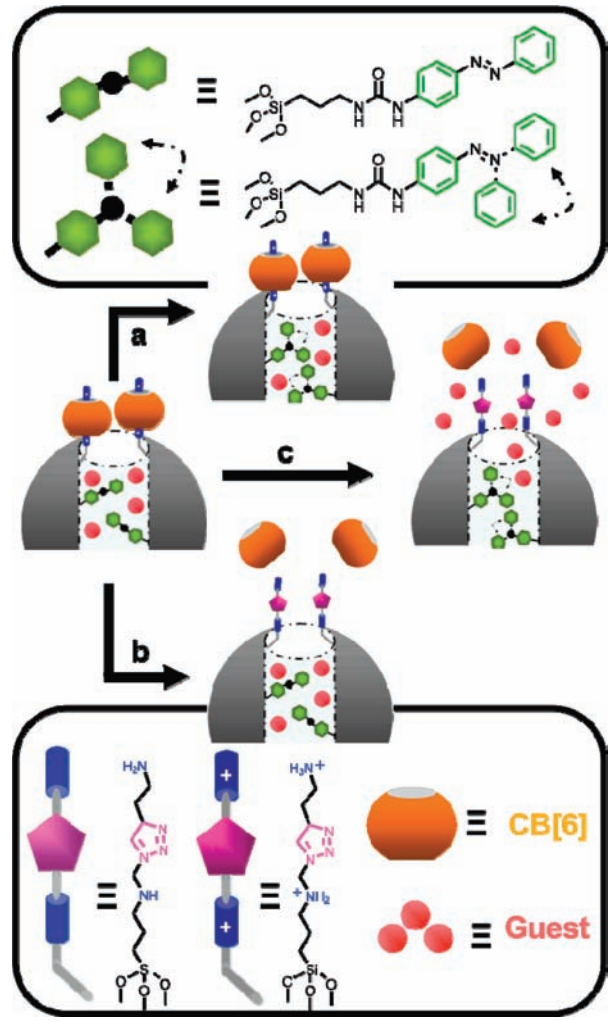

Figure 1. Operation of DCNP-**1**. (a) Excitation with 448 nm light induces the dynamic wagging motion of the nanoimpellers, but the nanovalves remain shut and the contents are contained. (b) Addition of NaOH opens the nanovalves, but the static nanoimpellers are able to keep the contents contained. (c) Simultaneous excitation with 448 nm light AND addition of NaOH causes the contents to be released.

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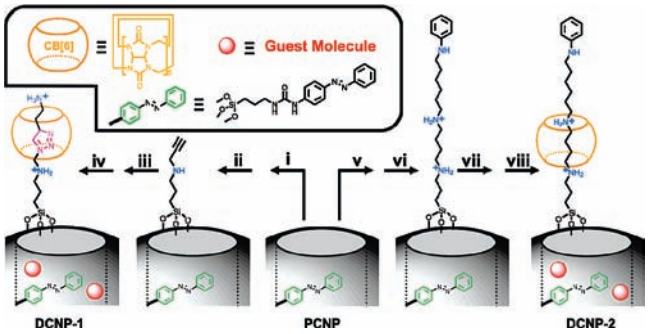
the stalks, thereby opening the nanovalves and allowing the contents to be released. The acid-responsive nanovalves used in DCNP-**2** consist of bistable CB[6]/trisammonium pseudorotaxanes. At neutral pH, the anilinium nitrogen atom remains unprotonated, and the CB[6] ring resides on the tetramethylenediammonium recognition unit close to the nanopore orifices. When the pH is decreased and the anilinium nitrogen atom becomes protonated, the CB[6] ring shuttles to the more distal hexamethylenediammonium recognition unit, and the nanovalves are opened.

Mesoporous silica nanoparticles prepared by a base-catalyzed sol−gel process were used as the solid supports for the molecular machines.[12,13] The nanoparticles were ∼400 nm in diameter and contained hexagonally arranged pores with a diameter of ∼2 nm. Mesoporous silica is an ideal support for synthetic molecular machines because it is optically transparent (allowing for activation by light and spectroscopic monitoring) and relatively easy to functionalize on both the insides of the pores and the outer surface.[14] Derivatization of the nanoparticles with the nanoimpellers and nanovalves was accomplished sequentially (Scheme 1) at different stages in the particle synthesis. First, the nanoimpellers were attached to the pore walls during the sol−gel synthesis to produce photocontrolled nanoparticles (PCNPs). Synthesis of the PCNPs was accomplished using a cocondensation method in which a silylated azobenzene derivative was added during the sol−gel synthesis and allowed to condense into the framework as the nanoparticles were formed. Cetyltrimethylammonium bromide (CTAB) surfactants were employed to template the nanopores, and tetraethylorthosilicate (TEOS) was used as the silica precursor. In order to derivatize the interior of the nanopores evenly, the azobenzene derivative, 4-phenylazoaniline, was first of all coupled to the linker molecule, isocyanatopropyltriethoxysilane (ICPES), and the azo-linker species was then added to the sol during nanoparticle synthesis and hence was incorporated onto the silica framework.[8d] The hydrophobic azobenzenes self-assembled into the CTAB micelles, ultimately becoming attached to the material at the interface between the micelle and the silica framework. The CTAB surfactant was removed by solvent extraction to yield empty nanopores with walls that were functionalized with azobenzene-based nanoimpellers. In order to achieve the dual functionality, pH-responsive nanovalves were next constructed on the surface of the PCNPs. First, amine-modification of the silica surface was accomplished by heating the nanoparticles in an aminopropyltriethoxysilane (APTES) solution under reflux.

Scheme 1. Syntheses of DCNP-**1** and DCNP-**2**[a]



[a] Conditions and reagents: (i, v) APTES, PhMe, 110 °C, 12 h; (ii) propargyl bromide, MeOH, 50 °C, 12 h; (iii, vii) 5 mM $ClRe(CO)_3$-2,2′-bipyridine, H_2O, RT, 24 h; (iv) CB[6], 2N HCl, RT, 3 days; (vi) $PhNH(CH_2)_6NH(CH_2)_4OTs$, MeOH, 50 °C, 2 days; (viii) CB[6], NaCl, 5 mM NaOH, RT, 3 days.

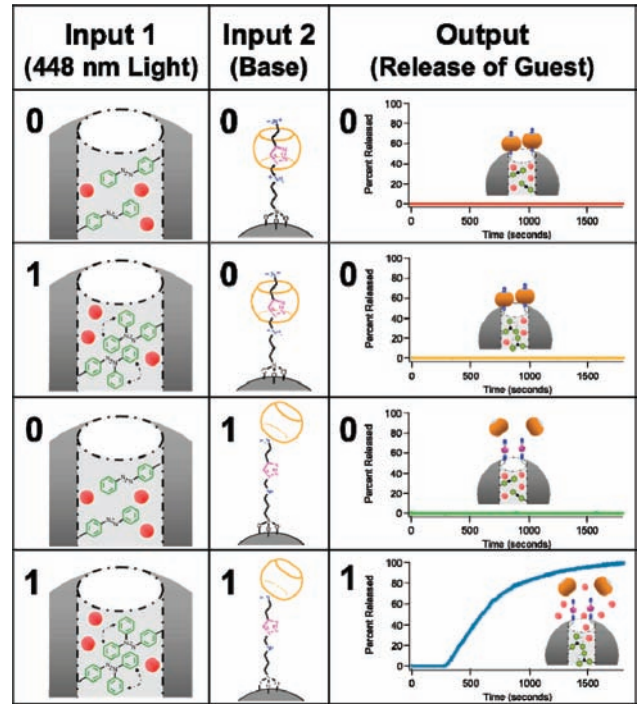


Figure 2. Truth table for an AND gate based on DCNP-**1**. Input 1 is excitation of the nanoimpellers by 448 nm light. Input 2 is the addition of NaOH to open the nanovalves. The output is the release of the guest, $ClRe(CO)_3$−2,2′-bipyridine.

In order to attach the base-responsive nanovalves to the surfaces of the nanoparticles, the amine-modified PCNPs were first treated with propargyl bromide to produce alkyne-terminated surfaces. The alkyne-terminated nanoparticles were then suspended overnight in a 0.5 mM solution of guest molecules to fill the empty impeller-lined pores with the guest molecules. Nanovalve synthesis was completed by employing CB[6]-catalyzed azide−alkyne 1,3-dipolar cycloaddition[15] of the tethered alkynes and 2-azidoethylamine to produce DCNP-**1**. Alternatively, the construction of DCNP-**2** was completed by (1) attaching a trisammonium stalk to the amine-modified surface, (2) loading guest molecules into the nanopores, and then (3) adjusting the pH of the system and threading CB[6] onto the stalks to close the nanovalves.

In order to test the operation of the dual-controlled systems, the DCNPs were loaded with the fluorescent probe $ClRe(CO)_3$−2,2′-bipyridine as the guest molecules, and luminescence spectroscopy was used to follow their fate. A small sample (∼10 mg) of the dye-loaded DCNPs was placed in the corner of a cuvette, which was then carefully filled with a 95% H_2O/5% EtOH solution (12 mL). A 4 mW, 448 nm probe beam was directed into the liquid and used to excite the dissolved dye molecules. After 5 min, one or both of the machines on the DCNP were activated. For the nanoimpellers, a 36 mW, 448 nm excitation beam was directed at the nanoparticles and used to activate the dynamic wagging of the azobenzenes. The nanovalves were opened by adjusting the pH appropriately. For DCNP-**1**, the solution was adjusted to pH 10 by the addition of 2 M NaOH, and for DCNP-**2**, the solution was adjusted to pH 4 by the addition of 0.01 M HCl. The emission spectrum of the dissolved dye was collected in 1 s intervals over a period of ∼30 min. The intensity at the emission maximum of $ClRe(CO)_3$−2,2′-bipyridine (562 nm) was plotted as a function of time to generate a release profile (Figure 2).

The release of $ClRe(CO)_3-2,2'$-bipyridine required activation of both the nanoimpellers and the nanovalves (Figure 2). When light or pH activation alone was used, activating just one machine, the unactivated machine was able to keep guest molecules constrained, and no release of guest molecules occurred. Only when both controlled release mechanisms were activated simultaneously was release observed. DCNP-**2** behaved similarly (as an AND gate) with use of HCl solution as input 2 (see the Supporting Information).

The DCNP systems reported here rely on light and pH inputs and function as AND logic gates. This research demonstrates the potential for using different mesoporous silica nanoparticle-supported molecular machines in tandem with one another to perform simple logic operations. For drug-delivery applications, the DCNP system introduces a method for attaining even more sophisticated levels of controlled release. By having one release mechanism operate in the presence of a specific biological trigger and having another release mechanism externally controlled, it might be possible to manually regulate the dosage delivered to a specific region. Various systems that could perform other operations can well be imagined. For example, a limit switch could be created by using a guest molecule designed in such a way that it could interact with one of the molecular machines when released, providing a feedback loop able to self-regulate the amount of the release.

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

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