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Light-Triggered Charge Reversal of Organic−Silica Hybrid Nanoparticles

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Supporting Information

ABSTRACT: A functional nanoparticle with light-triggered charge reversal based on a protected amine-bridged polysilsesquioxane was designed. An emulsion- and amine-free sol−gel synthesis was developed to prepare uniform nanospheres. Photolysis of suspensions of these nanoparticles results in a reversal of the ζ potential. This behavior has been used to trigger nanoparticle self-assembly, nanocomposite hydrogel formation, and nanoparticle release, showing the potential of this material in nanoscale manipulation and nanoparticle therapy.

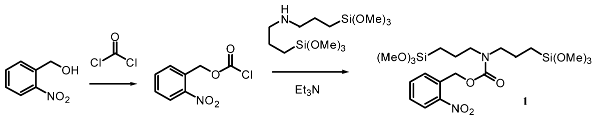
There has been substantial progress in the synthesis and applications of uniform, spherical bridged polysilsesquioxane (BPS) xerogel nanoparticles (NPs). Emulsion,[1] modified Stöber,[2] templated modified Stöber,[3] and self-assembly[4,5] methods were developed for NP synthesis from monomers spanning a range of water solubilities, shapes, and rigidity. Applications of BPS NPs include their use as photodeformable and photopatternable materials,[4] cellular-imaging NPs,[6] and the active component in solid-state electrochromic devices.[7]

Both inorganic and organic moieties can contribute significantly to the colloidal charge of BPS NPs. While uncondensed silanol groups ($pK_a \approx 4$) generally provide abundant negative charge at pH 5 or higher, recent findings[2] have shown that functional organic bridging groups (e.g., alkylamines) may contribute positive charge that only partially compensates for the surface negative charge (negative ζ potential) under basic conditions but eventually dominates the surface charge (positive ζ potential) under neutral or acidic conditions. This phenomenon offers the potential to modulate the colloidal charge over a wide range.

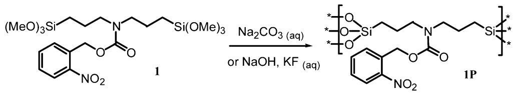
The self-assembly of NPs based on charge interactions has been proven to be one of the most effective and reliable strategies for the fabrication of novel nanostructured materials. The methods range from layer-by-layer assembly[8] for planar or colloidal structures[9] to NP "complexes",[10] superlattices or crystals,[11] and nanocomposites.[12] Applications include electronic devices,[13] HPLC stationary phases,[14] solar cells,[15] imaging quantum dots,[16] self-healing hydrogels,[17] and therapeutic NPs.[18]

NPs with charge-reversal capability have recently attracted attention in the release of therapeutic agents triggered by pH change[19,20] or UV irradiation.[21,22] The strength of the latter strategy lies in its site and time specificity. However, most current research in the field is focused on triggered release of therapeutic small molecules or nucleic acids *from* NPs. The release *of* therapeutic NPs that function by "direct interaction" (such as those that capture toxins[23] or disrupt deleterious cells[24]) still remains a challenge. In this study, we report a novel type of BPS NP with charge-reversal functionality triggered by a photochemical reaction and model studies suggesting its applications in fields such as nanomaterial self-assembly and nanoparticle therapy. The design of our nanomaterials features a negative colloidal charge that is intrinsic to the as-synthesized BPS NPs. Upon UV irradiation, secondary amine groups emerge in the bridging moieties, reversing the overall colloidal charge from negative to positive. BPS NPs with *o*-nitrobenzyl carbamate-protected amine[25] bridging groups were chosen as the photoresponsive material to demonstrate this concept.

To prepare the precursor for the nanomaterials, *o*-nitrobenzyl chloroformate[26] was slowly added to a solution of equimolar bis(trimethoxysilylpropyl)amine and excess Et_3N at −12 °C. NMR analysis of the reaction mixture showed full consumption of the chloroformate with ∼3 mol % decomposed chloroformate and ∼3 mol % unreacted monomer. A corresponding amount of the chloroformate was added. This procedure yielded *o*-nitrobenzyl-*N*,*N*-bis(trimethoxysilylpropyl) carbamate (**1**), the monomer for the photoresponsive BPS materials (eq 1).



(1)



(2)

Typical sol−gel syntheses of SiO_2 or organic-silica hybrid NPs involve reaction in aqueous ammonia solution. Since the carbamate group is known to be unstable in the presence of NH_3, a protocol for base-catalyzed BPS NP synthesis without highly nucleophilic reagents was needed. The synthesis of uniform, spherical BPS NPs (**1P**) from monomer **1** was achieved in aqueous solution containing catalysts such as Na_2CO_3, NaOH, and KF and 1-PrOH as a a cosolvent (eq 2 and Table 1). Model studies using *o*-nitrobenzyl-*N*,*N*-diethyl carbamate in the catalyst solutions showed no reaction of the starting material, suggesting that the carbamate bridging moiety would be stable under these polymerization conditions.

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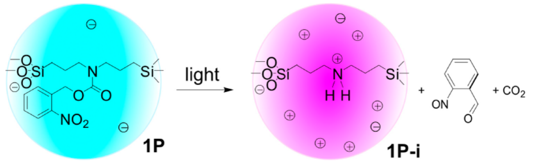
Table 1. Amine-Free Modified Stöber Synthesis and Size Control of BPS NPs **1P** (A Recipe for Finer Size Control Is Included in the Supporting Information)

[Na_2CO_3] (mM)	[NaOH] (mM)	[KF] (mM)	1-PrOH (%)	[**1**] (mM)	T (°C)	D_n (nm)[a]
20	0	0	0	50	60	400
10	0	0	0	20	25	200
10	0	0	10	20	25	260
25	0	0	0	20	25	160
0	5.0	10	0	10	25	83
0	5.0	20	5	10	25	110
0	7.5	0	0	10	25	42
0	7.5	10	0	10	25	63

[a] Number-average diameter determined by DLS. All DLS measurements gave a polydispersity index (PDI) of <0.09, suggesting monodisperse NPs.

Suspensions of dialyzed carbamate-BPS NPs were irradiated with a hand-held UV lamp (4 mW/cm^2 of 254 nm UV light). Little change in particle size was observed by dynamic light scattering (DLS), and the ζ potential was reversed from negative to positive upon irradiation (Scheme 1 and Figure 1a).

Scheme 1. Light-Triggered Charge Reversal and Chemistry of **1P** NPs



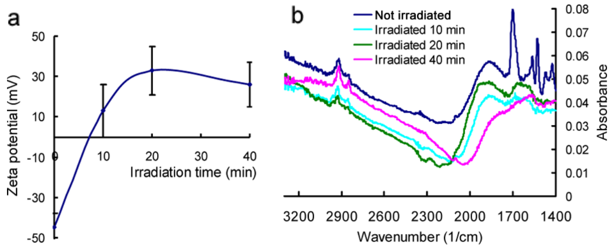
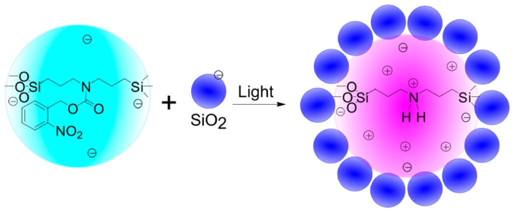


Figure 1. (a) ζ potential measurements of suspensions of **1P** NPs after UV irradiation for various durations. **1P** NPs of various sizes generally gave nearly identical results. (b) IR spectra of **1P** and **1P-i** NPs with various durations of UV irradiation in water suspension.

This experiment showed that 10 min of UV irradiation with a hand-held UV lamp was sufficient for reversal of the colloidal charge. This was confirmed by the IR spectra of **1P** and **1P-i** NPs drop-coated on a CaF_2 plate. Samples prepared from suspensions of **1P** exhibited absorptions at 1698 cm^{-1} (C═O) and 1530 cm^{-1} (NO_2). After irradiation for 10 min or longer, these absorptions were no longer detectable (Figure 1b).

An application of light-triggered colloidal charge reversal was demonstrated by the triggered self-assembly of nanomaterials. A suspension of **1P** (with number- and volume-average diameters D_n = 160 nm and D_v = 200 nm, respectively) and SiO_2 NPs (70 nm, prepared by the published Stöber process) was prepared by mixing deionized water suspensions of the two types of NP. We expected that without UV irradiation, the negatively charged BPS NPs and SiO_2 NPs would show little affinity for each other. However, upon UV irradiation, the BPS NPs would be transformed into species with a positive ζ potential, providing the potential for self-assembly of a shell of SiO_2 NPs on the surface of the BPS NPs (Scheme 2).

Scheme 2. Light-Triggered "NP Shell" Assembly



The expectation from the preceding experimental design was supported by DLS measurements. The volume average of "large NPs" in the presence of 70 nm SiO_2 particles showed a significant increase in size after irradiation, with D_v increasing to ~260 nm (Figure S4 in the Supporting Information; D_n increased to 230 nm). Since the diameter measured by DLS is an "equivalent spherical" (or "same-size sphere") diameter,[27] such a size increase corresponds to close to a monolayer of 70 nm SiO_2 NPs assembled on the BPS NPs. The volume ratio between "large NPs" and SiO_2 NPs showed an over-representation of the former in both mixtures and thus is less representative of the difference between the irradiated and non-irradiated mixtures. SEM images of a better "visualized" example obtained by using larger **1P** NPs is presented in Figure 2.

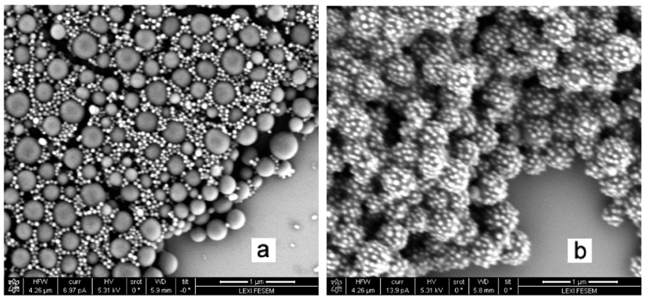
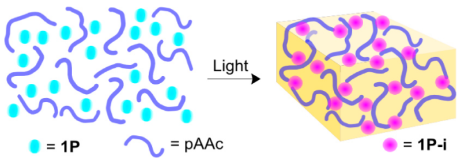


Figure 2. SEM image of centrifuged, resuspended, and dried mixture suspension of **1P** (260 nm) and SiO_2 NPs (70 nm) (a) before and (b) after UV irradiation. Scale bar: 1 μm.

The light-triggered self-assembly phenomenon could also be applied in the formation of a bulk nanocomposite hydrogel (Scheme 3). A mixture containing **1P** NPs (D_n = 42 nm) and poly(acrylic acid) (pAAc, MW = 1.0 × 10^6, pH adjusted to 8.1 by KOH) appeared as a viscous fluid. With UV irradiation, the mixture turned into a nanocomposite hydrogel that was soft but held its own weight and kept its shape even after being stored upside down for more than 2 weeks (Figure 3). This is

Scheme 3. Light-Triggered "Nanocomposite Hydrogel" Assembly



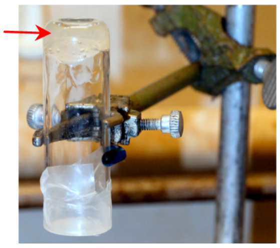
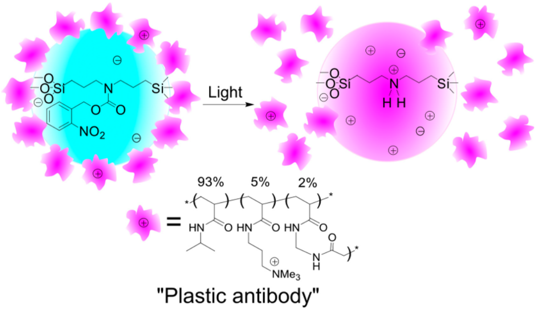


Figure 3. Photograph of a mixture of **1P** NPs (D_n = 42 nm) and aqueous pAAc (K^+ salt), stored as shown for 14 days after UV irradiation.

attributed to cross-linking of the linear polyanion by the positively charged **1P-i** NPs (converted from negatively charged **1P** NPs) through charge interactions. It is also noteworthy that the total non-water mass percent in the hydrogel network was ~0.2%. An optimized version of the nanocomposite hydrogel may exhibit properties such as high mechanical toughness and self-healing[17] and provide applications in fields such as tissue engineering[28] and catalytic hydrogels.[29] These applications are currently under investigation.

Scheme 4. Light-Triggered Release of "Plastic Antibody" NPs



The triggered release of functional NPs could also be accomplished by the BPS NPs with light-triggered charge-reversal capability. (Scheme 4) "**PA+74**" NPs (74 nm, ζ potential = +37 ± 7 mV) belong to a family of therapeutic polymer hydrogel NPs with antibody-like affinity for peptides.[30,31] **1P** (D_n = 160 nm) was slowly added into a suspension of **PA+74** NPs. After mixing and sonication, the suspension consisted of **1P** NPs loaded with **PA+74** NPs in excess. We expected that charge reversal of **1P** NPs induced by UV irradiation would trigger release of the **PA+74** NPs by charge repulsion.

The expectation from this experimental design was supported by DLS data. The size of **1P** NPs loaded with **PA+74** (D_n = 255 nm, D_v = 340 nm; minor aggregation among multiple **1P** and **PA+74** NPs may have occurred during the loading process) showed a significant decrease after irradiation (Figure S6; D_n = 201 nm, D_v = 238 nm). The volume contributed by **PA+74** NPs, although underrepresented by DLS in both samples, also increased from 31% in the non-irradiated sample to 37% in the irradiated sample. Overall, the size distribution difference between the irradiated and non-irradiated mixtures suggests that the release of **PA+74** NPs from the surface of **1P** NPs triggered by UV irradiation takes place with significant efficiency. This experiment suggests the possibility of triggered release of therapeutic NPs. Optimization of materials for cell and tissue experiments is under investigation.

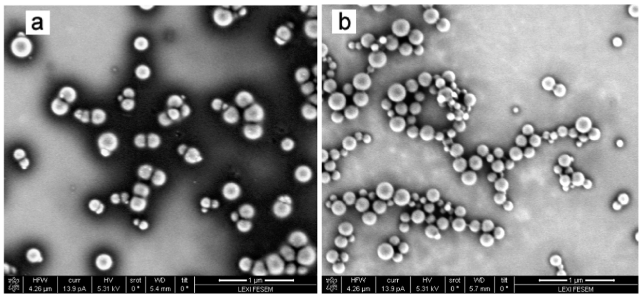


Figure 4. SEM images of centrifuged, resuspended, and dried **1P** NPs (D_n = 160 nm) assembled with **PA+74** NPs (a) without and (b) with UV irradiation in H_2O suspension. The dark region in (a) is dried **PA+74** (lightly cross-linked hydrogel) NPs (Figure S6).

Hydrogel NPs (**PA+74**) remained suspended in the supernatant under centrifugation while BPS NPs were deposited as a solid. This difference was utilized to visualize the light-triggered release. Without irradiation, the SEM image of the NP complex collected by centrifugation showed organic **PA+74** NPs collected along with **1P** NPs. Following light-triggered release, the image suggested that **PA+74** was no longer associated with **1P-i** (Figure 4). An experiment using fluorescence-labeled **PA+74** NPs confirmed this observation. The hydrogel NPs were released into water as a stable suspension after the light-triggered release. With UV irradiation, far more fluorescent hydrogel NPs stayed in the supernatant rather than being removed by centrifugation with **1P** NPs, providing the supernatant with higher fluorescence intensity (Figure 5).

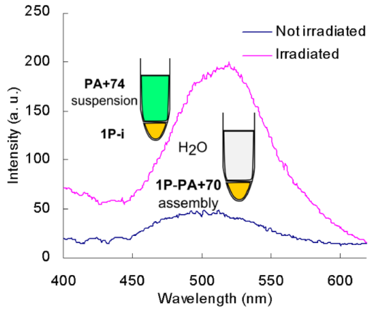


Figure 5. Fluorescence spectrum (λ_{ex} = 330 nm) of the supernatant after a centrifugation that removed **1P** loaded with **PA+74** NPs from the suspension (blue). The **1P–PA+74** assembly was isolated from the excess **PA+74** prior to the experiment. The same sample was then redispersed, UV-irradiated, and centrifuged, and the fluorescence spectrum of the resulting supernatant was taken (pink).

In this research, we have demonstrated the first amine-free modified Stöber synthesis of uniform bridged polysilsesquioxane NPs (and size control strategies), the design and synthesis of photoresponsive organic–silica hybrid NPs, and their function of light-triggered charge reversal. We have also accomplished light-triggered NP self-assembly, nanocomposite hydrogel formation, and NP release based on the light-triggered charge reversal of the BPS NPs. Our strategy and materials have been shown to be compatible with organic or inorganic, soft or rigid NPs as well as linear polymers. Thus, this research reveals a novel strategy for nanoscale manipulation with good potential for applications that include controlled formation of nanostructured materials and nanocomposites as well as release of polymer and NP drugs.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed synthesis and characterization data as well as experimental procedures and data supporting the statements about the function of materials. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Khiterer, M.; Shea, K. J. *Nano Lett.* **2007**, *7*, 2684−2687.

(2) Hu, L. C.; Khiterer, M.; Huang, S. J.; Chan, J. C. C.; Davey, J. R.; Shea, K. J. *Chem. Mater.* **2010**, *22*, 5244−5250.

(3) Urata, C.; Yamada, H.; Wakabayashi, R.; Aoyama, Y.; Hirosawa, S.; Arai, S.; Takeoka, S.; Yamauchi, Y.; Kuroda, K. *J. Am. Chem. Soc.* **2011**, *133*, 8102−8105.

(4) Zhao, L.; Loy, D. A.; Shea, K. J. *J. Am. Chem. Soc.* **2006**, *128*, 14250−14251.

(5) Lu, Y. F.; Fan, H. Y.; Doke, N.; Loy, D. A.; Assink, R. A.; LaVan, D. A.; Brinker, C. J. *J. Am. Chem. Soc.* **2000**, *122*, 5258−5261.

(6) Faisal, M.; Hong, Y.; Liu, J.; Yu, Y.; Lam, J. W.; Qin, A.; Lu, P.; Tang, B. Z. *Chem.—Eur. J.* **2010**, *16*, 4266−4272.

(7) Jain, V.; Khiterer, M.; Montazami, R.; Yochum, H. M.; Shea, K. J.; Heflin, J. R. *ACS Appl. Mater. Interfaces* **2009**, *1*, 83−89.

(8) Ariga, K.; Hill, J. P.; Ji, Q. *Phys. Chem. Chem. Phys.* **2007**, *9*, 2319−40.

(9) Caruso, F.; Caruso, R. A.; Mohwald, H. *Science* **1998**, *282*, 1111−1114.

(10) Kolny, J.; Kornowski, A.; Weller, H. *Nano Lett.* **2002**, *2*, 361−364.

(11) Kalsin, A. M.; Fialkowski, M.; Paszewski, M.; Smoukov, S. K.; Bishop, K. J.; Grzybowski, B. A. *Science* **2006**, *312*, 420−424.

(12) Tanami, G.; Gutkin, V.; Mandler, D. *Langmuir* **2010**, *26*, 4239−4245.

(13) Javey, A.; Nam, S.; Friedman, R. S.; Yan, H.; Lieber, C. M. *Nano Lett.* **2007**, *7*, 773−887.

(14) Dun, H.; Zhang, W.; Wei, Y.; Xiuqing, S.; Li, Y.; Chen, L. *Anal. Chem.* **2004**, *76*, 5016−5023.

(15) He, J. A.; Mosurkal, R.; Samuelson, L. A.; Li, L.; Kumar, J. *Langmuir* **2003**, *19*, 2169−2174.

(16) Mackay, P. S.; Kremers, G. J.; Kobukai, S.; Cobb, J. G.; Kuley, A.; Rosenthal, S. J.; Koktysh, D. S.; Gore, J. C.; Pham, W. *Nanomedicine* **2011**, *7*, 489−496.

(17) Wang, Q.; Mynar, J. L.; Yoshida, M.; Lee, E.; Lee, M.; Okuro, K.; Kinbara, K.; Aida, T. *Nature* **2010**, *463*, 339−343.

(18) Poon, Z.; Chang, D.; Zhao, X.; Hammond, P. T. *ACS Nano* **2011**, *5*, 4284−4292.

(19) Xu, P.; Van Kirk, E. A.; Zhan, Y.; Murdoch, W. J.; Radosz, M.; Shen, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 4999−5002.

(20) Guo, S.; Huang, Y.; Jiang, Q.; Sun, Y.; Deng, L.; Liang, Z.; Du, Q.; Xing, J.; Zhao, Y.; Wang, P. C.; Dong, A.; Liang, X. J. *ACS Nano* **2010**, *4*, 5505−5511.

(21) Han, G.; You, C. C.; Kim, B. J.; Turingan, R. S.; Forbes, N. S.; Martin, C. T.; Rotello, V. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 3165−3169.

(22) Vivero-Escoto, J. L.; Slowing, I. I.; Wu, C. W.; Lin, V. S. *J. Am. Chem. Soc.* **2009**, *131*, 3462−3463.

(23) Hoshino, Y.; Kodama, T.; Okahata, Y.; Shea, K. J. *J. Am. Chem. Soc.* **2008**, *130*, 15242−15243.

(24) Nederberg, F.; Zhang, Y.; Tan, J. P.; Xu, K.; Wang, H.; Yang, C.; Gao, S.; Guo, X. D.; Fukushima, K.; Li, L.; Hedrick, J. L.; Yang, Y. Y. *Nat. Chem.* **2011**, *3*, 409−414.

(25) Cameron, J. F.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1991**, *113*, 4303−4313.

(26) Singh-Gasson, S.; Green, R. D.; Yue, Y.; Nelson, C.; Blattner, F.; Sussman, M. R.; Cerrina, F. *Nat. Biotechnol.* **1999**, *17*, 974−978.

(27) Schärtl, W. *Light Scattering from Polymer Solutions and Nanoparticle Dispersions*; Springer: Berlin, 2007.

(28) Chang, C. W.; van Spreeuwel, A.; Zhang, C.; Varghese, S. *Soft Matter* **2010**, *6*, 5157−5164.

(29) Das, A. K.; Collins, R.; Ulijn, R. V. *Small* **2008**, *4*, 279−287.

(30) Hoshino, Y.; Koide, H.; Urakami, T.; Kanazawa, H.; Kodama, T.; Oku, N.; Shea, K. J. *J. Am. Chem. Soc.* **2010**, *132*, 6644−6645.

(31) Hoshino, Y.; Koide, H.; Furuya, K.; Haberaecker, W. W., III; Lee, S. H.; Kodama, T.; Kanazawa, H.; Oku, N.; Shea, K. J. *Proc. Natl. Acad. Sci. U.S.A.* **2012**, *109*, 33−38.