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Responsive Polymer-Coated Mesoporous Silica as a pH-Sensitive Nanocarrier for Controlled Release

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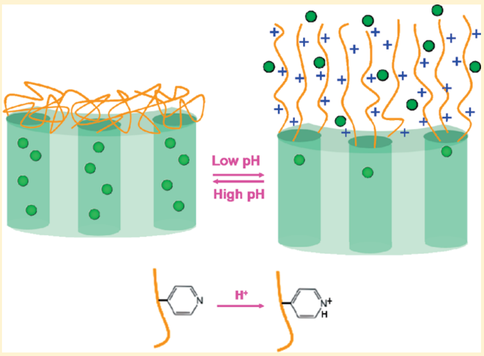
S *Supporting Information*

ABSTRACT: pH-responsive polymer poly(4-vinyl pyridine) is coated on mesoporous silica through the facile "grafting to" method. The grafted polymer nanoshell can work as a pH-sensitive barrier to control the release of trapped molecules from mesoporous silica.



INTRODUCTION

The ability to trap and release molecules from mesoporous silica nanoparticles holds promise in sensor and drug-delivery applications.[1] The great diversity in surface functionalization of mesoporous silica offers a unique advantage in the construction of nanogates responsive to different stimuli. Various types of nanoparticles,[2] organic molecules,[3] and biomolecules,[4] have been used as capping agents to block molecule transport from a silica mesopore and to unlock the entrance for triggered release under specific external stimuli. A combination of mesoporous silica with functional polymers generates a novel type of hybrid nanoswitch that takes advantage of the unique features of polymers and porous materials. Thermosensitive poly(*N*-isopropylacrylamide) coated on mesoporous silica could control the molecule release at different temperatures.[5] Poly(acrylic acid) was grafted onto the exterior surface of mesoporous silica by reversible addition—fragmentation chain-transfer (RAFT) polymerization and works as a smart nanovalve sensitive to pH changes.[6] Poly(2-(diethylamino)ethyl methacrylate) was also anchored on mesoporous silica by atom transfer radical polymerization (ATRP) for pH-controlled release.[7] Our group introduced a cross-linkable polymer into a mesoporous silica release system and prepared a new type of versatile responsive system.[8] The pores of guest molecules with loaded silica materials are blocked by the addition of cystamine, a disulfide-based bifunctional primary amine, which allows polymer chains around the silica surface to be cross-linked. 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.[8a] The cyclodextrins are further introduced into the polymer network and expand responsive diversity by photoirradiation, redox signal, and competitive supramolecular binding.[8b]

Most reported polymer—mesoporous silica hybrid materials use a "grafting from" method and involve complicated polymerization on the surface. Although there was few reports for modifying mesoporous silica using the direct "grafting to" method,[5b] it also involved a laborious pre-polymerization process. Here, we use a simple "grafting to" method to facilely modify the silica surface with a commercially available responsive polymer to fabricate a novel type of pH-sensitive controlled release materials. The responsive polymer used here is commercially available poly(4-vinyl pyridine) (PVP). PVP has been widely used in the construction of responsive colloid and surface systems because of its pH-triggered switching ability. For example, PVP-brush-functionalized indium tin oxide (ITO) electrode allowed for the reversible transition of the electrode interface between the active and inactive states because of the reversible restructuring of the polymer brush induced by the local interfacial pH changes.[9] PVP has also been used to direct the reversible formation of nanoparticle aggregates by tuning the pH of the particle aqueous suspensions.[10] In our system, we anchor PVP on mesoporous silica by simply grafting PVP with a bromo-functionalized silica surface. As shown in Scheme 1, at high pH, the deprotonation of the polymer produces a hydrophobic shrunken state and inhibits the release of trapped molecules. The swollen state of the protonated PVP at low pH is permeable to molecule transport, leading to the pH-controlled release.

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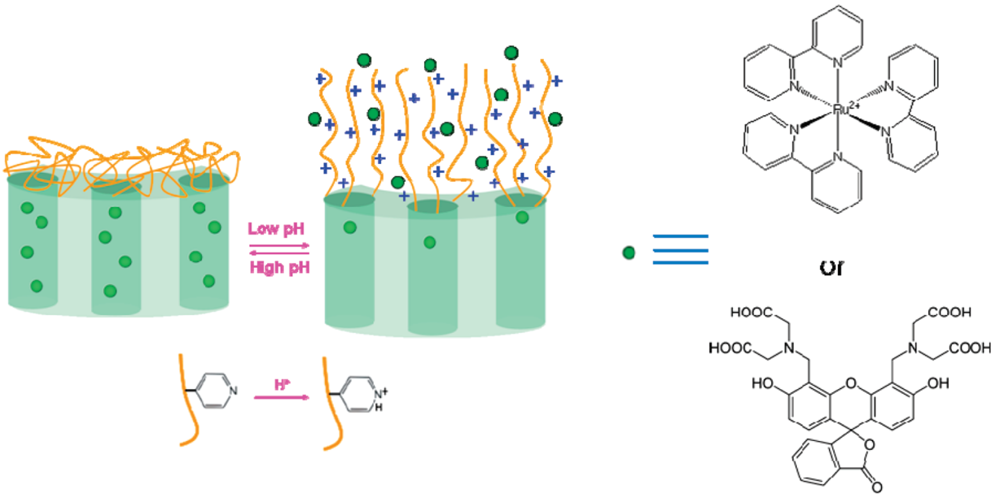
Scheme 1. pH-Controlled Release from Responsive Polymeric Nanoshell-Coated Mesoporous Silica



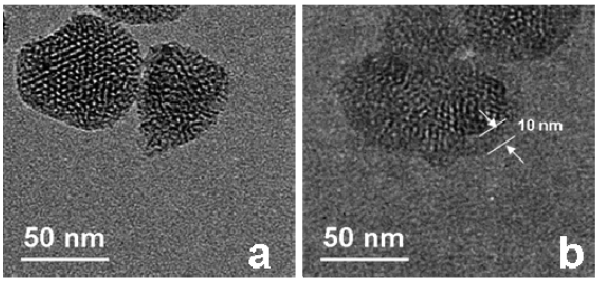


Figure 1. TEM of (a) Br−MS and (b) PVP−MS.

■ EXPERIMENTAL SECTION

MCM-41-Type Mesoporous Silica Particles. MCM-41 was synthesized according to literature procedures:[2a] *n*-Cetyl-trimethylammonium bromide (CTAB, 1.0 g) was dissolved in 480 mL of distilled water. NaOH (aqueous) (2.00 M, 3.50 mL) was added to CTAB solution, and the solution temperature was adjusted to 80 °C. Triethoxysilane (5.00 mL) was added dropwise to the solution, and the mixture was allowed to stir for 2 h at 80 °C. The resultant white precipitate was isolated by filtration. The silica particles were then calcined at 550 °C for 5 h to remove the template.

PVP-Functionalized Mesoporous Silica (PVP−MS). A total of 50 mg of MCM-41 was reacted with 0.05 mL of bromomethyldimethylchlorosilane in 5 mL of toluene for 20 min at 70 °C to give bromo-functionalized mesoporous silica (Br−MS). A short reaction time makes the attachment of the functional group to the pore outlets rather than their inside walls.[11] A total of 5 mg of Br−MS was reacted with 15 mg of PVP (MW of 60 000, Sigma-Aldrich) in 1 mL of nitromethane at 50 °C for 60 h. The solid was repeatedly washed by nitromethane and water to give rise to PVP−MS.

Characterization. N_2 sorption analysis was performed on a Micromeritics ASAP2010 volumetric adsorption analyzer at 77 K. ζ-Potential analysis was performed on a ZetaPALS system. Transmission electron microscopy (TEM) images were recorded on a Philips Tecnai 12 transmission electron microscope. Fourier transform infrared (FTIR) spectra were performed on Bruker Equinox 55 with KBr plates. Thermogravimetric analysis (TGA) was carried out on TA Q500 under flowing N_2 at a heating rate of 10 °C/min.

Loading, Capping, and Release Experiments. Br−MS (5 mg) was stirred in 1 mL of 0.1 mg/mL $[Ru(bipy)_3]Cl_2$ solution in nitromethane at room temperature for 60 h. Then, PVP (15 mg) was added to the suspension. The mixture was stirred at 50 °C for another 60 h. The precipitate was centrifuged and washed extensively with nitromethane and water. The final absorbance is 18%. To investigate the pH-responsive properties, a dye-loaded particle (1.0 mg) was dispersed in 1 mL of water at a certain pH. The release of the $Ru(bipy)_3^{2+}$ dye from the pore was monitored via the spin-allowed d−π metal-to-ligand charge-transfer transition band of the $Ru(bipy)_3^{2+}$ dye centered at 454 nm. The control experiments were carried out by soaking 5 mg of Br−MS in 1 mL of 0.1 mg/mL $[Ru(bipy)_3]Cl_2$ solution in nitromethane at room temperature for 60 h before the precipitate was centrifuged and washed extensively with water, and then 1 mg of particle was dispersed in 1 mL of water at different pH values to test the release property. The adsorpsion, capping, and release of negative dye calcein were tested using the similar procedure.

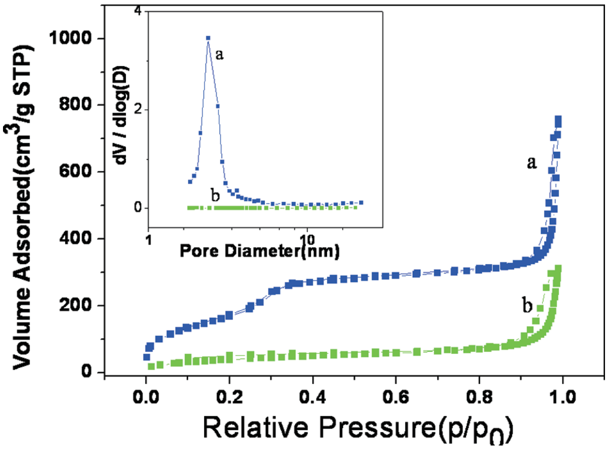


Figure 2. BET nitrogen sorption isotherms and (inset) Barrett−Joyner−Halenda (BJH) pore size distribution plots of (a) Br−MS and (b) PVP−MS.

■ RESULTS AND DISCUSSION

Mesoporous silica MCM-41 is synthesized according to the reported method.[2a] The obtained MCM-41 was then reacted with bromomethyldimethylchlorosilane to yield a bromo-functionalized mesoporous silica (Br−MS).[9] The honeycomb-like

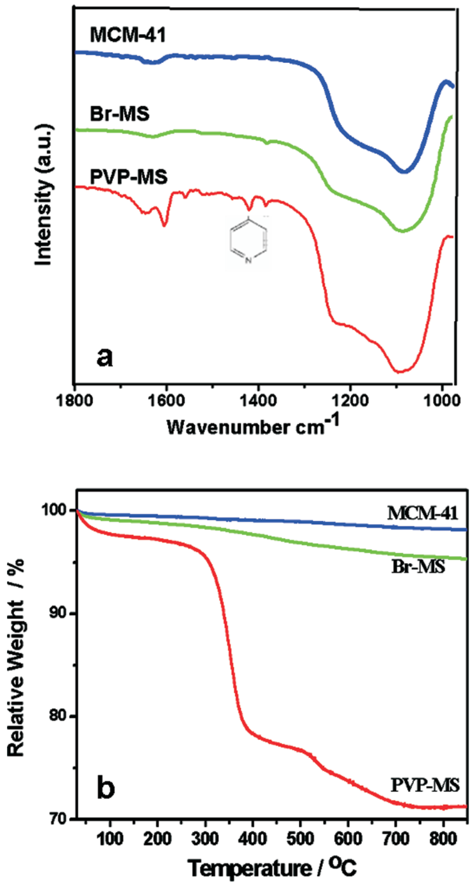


Figure 3. (a) FTIR and (b) TGA of MCM-41, Br—MS, and PVP—MS.

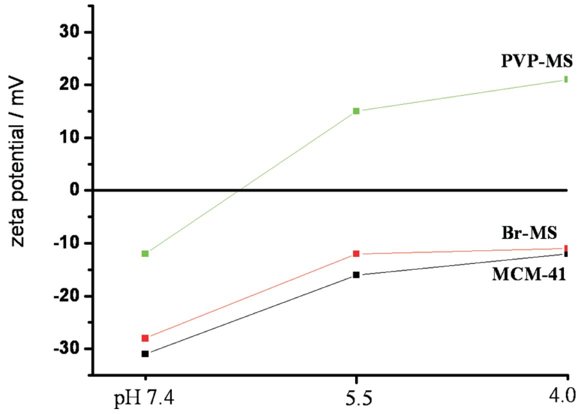


Figure 4. ζ-Potential change of MCM-41, Br—MS, and PVP—MS at different pH values.

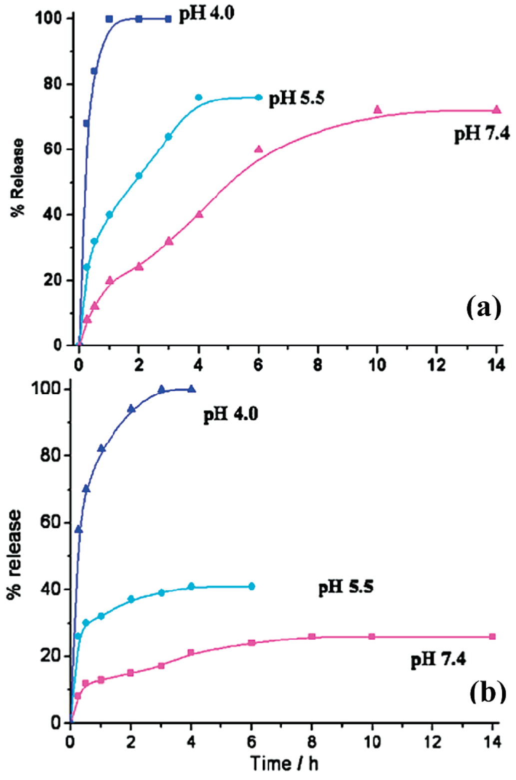


Figure 5. Time course of (a) $[\mathrm{Ru(bipy)_3}]\mathrm{Cl_2}$ and (b) calcein release from PVP—MS at different pH values.

structure of Br—MS was confirmed by TEM (Figure 1a), with a Brunauer—Emmett—Teller (BET) surface area of 640 m^2/g and average pore diameter of 2.5 nm from N_2 sorption analysis (Figure 2a). PVP was grafted to the functionalized silica surface through quaternized pyridine groups,[9] yielding tethered polymer layers on the exterior surface of MCM-41 (denoted as PVP—MS; see the Experimental Section and Scheme S1 in the Supporting Information). The successful grafting of polymer onto mesoporous silica was confirmed by the appearance of the band at 1414 cm^{-1} in the FTIR spectroscopy (Figure 3a), which is characteristic of the pyridine group of PVP. TGA of PVP—MS yielded about 30% weight loss from the grafted polymer when heating in a N_2 atmosphere to 800 °C, while 4% weight loss was observed for Br—MS and almost no weight loss for pure MCM-41 in the same temperature range (Figure 3b). TEM in Figure 1b showed that PVP—MS remained in the honeycomb-like pore structure as Br—MS, and a 10 nm dense polymer coating was observed around the silica particle after grafting. Although the N_2 sorption measurement of Br—MS exhibited typical type-IV isotherms of mesoporous materials (Figure 2a), PVP—MS showed an isotherm characteristic of nonporous materials (Figure 2b). The change of sorption type together with the decrease of the surface area and pore size distribution indicated the capping effect of the coated polymer.

pH-responsive PVP grafted on the mesoporous silica endows the hybrid material novel pH sensibility. ζ potential was monitored in Figure 4 to track the surface property of three materials. As shown in Figure 4, pure MCM-41 gave all negatively charged surfaces at pH 7.4, 5.5, and 4.0, matching well with the reported isoelectric point (pH 2—3) of mesoporous silica.[12] Br—MS showed the similar change trend. However, the presence of PVP drastically changed the surface property. At pH 7.4, the surface is still negative, while the ζ potentials of hybrid materials are 15.3 ± 2.9 and 20.9 ± 0.8 mV at pH 5.5 and 4.0, respectively. In comparison to MCM-41 and Br—MS, the positively charged surface at low pH is believed to come from responsive PVP, in which the apparent pK_a of 4-vinyl pyridine is 5.39.[13]

To investigate the pH-responsive gating behavior of the hybrid nanomaterials, dye $[\mathrm{Ru(bipy)_3}]\mathrm{Cl_2}$ (bipy = 2,2-bipyridine), as a guest, was first loaded by soaking Br—MS in $[\mathrm{Ru(bipy)_3}]\mathrm{Cl_2}$ nitromethane solution. Then, PVP was added to the mixture to coat the mesoporous silica. The excessive dye was removed by centrifugation and repeated washing with nitromethane and water. The resulting particles were then dispersed in water at different pH values to test their controlled release property (Figure 5a). At pH 7.4, the existing free space or volume between the polymer chains allows for the slow release of dye, and it needs 14 h to reach 70% release, indicating the capping effect of the coated polymeric barrier. The pH 5.5 environment induced the fast release of dye molecules, and the release profile in Figure 5a exhibited that the release reached 70% at 6 h and no more release was observed after that. The release profile in Figure 5a exhibited the fastest molecular transport at pH 4.0, in which 100% release and a final concentration of 2.08 μM were obtained within 1 h.

To eliminate the inherent charge effect of coated polymer on the release of the positive dye, negatively charged dye calcein was also used for model molecules to test the responsive gating effect. The release kinetics in Figure 5b showed a similar trend with $[Ru(bipy)_3]Cl_2$. The saturated releasing calcein concentration at pH 4.0 was 1.70 μM. The effect of the pH value on the releasing property of both dye molecules is strongly related to the protonation degree of pyridine groups of PVP at different pH values. At pH 7.4, a neutral shrunken hydrophobic polymer works as a collapsed monolayer and does not allow for the fast molecule penetration. The decrease of pH induces polymer swelling associated with the ionized pyridine groups. The stretched swollen layer starts to be permeable for the trapped molecule. Judging from the apparent pK_a of 5.39 of 4-vinyl pyridine and ζ potential discussed above, the pyridine groups become fully protonated at pH 4.0. The fully positively charged and swollen hydrophilic state of the surface-tethered polymer layer allows for quick transportation of dye from mesoporous silica and leads to the fastest release at pH 4.0. To further demonstrate the capping effect of pH-dependent coated PVP, control experiments were carried out. Br−MS was used as a nanocontainer to trap both dye molecules without further capping PVP. No molecule was released in both cases at pH 7.4, 5.5, and 4.0 because the absorbed molecules escaped from unguarded pores or the external surface during the extensive washing steps, which again confirm that the pH-responsive capping ability comes from the responsive polymer. Because some drugs, such as oxindolimine−copper(II) complexes or cromoglicic acid, have the similar chemical structures with model dyes used here, the system reported can be potentially used for the responsive release of these drugs.

CONCLUSION

In conclusion, we report here the controlled release of guest molecules from mesoporous silica particles using PVP as a pH-responsive capping nanoshell. We use a simple "grafting to" method to tether PVP onto the mesoporous silica surface, and a surface-tethered polymer layer works as a permission barrier of molecule transport from the mesopore at neutral pH. A lower pH induces quick release because the protonation polymer becomes swollen and permeable to the trapped molecule. The releasing kinetics is dependent upon the protonation degree of PVP at different pH values. The results make the system reported here promising candidates in the formulation of a pH-sensitive vehicle in *in vivo* delivery of therapeutic contents to low pH tissues, such as tumors and inflammatory sites. It is expected that, by increasing the polymer density or polymer chain length, the leakage at physiological pH could be decreased to a minimum. This approach could also provide a general route to graft other sensitive polymers onto the surface of silica particles for a wide range of different applications.

ASSOCIATED CONTENT

S Supporting Information. Schematic outline of the synthesis of PVP−MS (Scheme S1). This material is available free of charge via the Internet at http://pubs.acs.org.

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REFERENCES

(1) (a) Trewyn, B. G.; Slowing, I. I.; Giri, S.; Chen, H.; Lin, V. S.-Y. *Acc. Chem. Res.* **2007**, *40*, 846. (b) Slowing, I. I.; Trewyn, B. G.; Giri, S.; Lin, V. S.-Y. *Adv. Funct. Mater.* **2007**, *17*, 1225. (c) Trewyn, B. G.; Giri, S.; Slowing, I. I.; Lin, V. S.-Y. *Chem. Commun.* **2007**, 3236. (d) Vallet-Regi, M.; Balas, F.; Acros, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 7548.

(2) (a) Lai, C.-Y.; Trewyn, B. G.; Jeftinija, D. M.; Jeftinija, K.; Xu, S.; Jeftinija, S.; Lin, V. S.-Y. *J. Am. Chem. Soc.* **2003**, *125*, 4451. (b) Giri, S.; Trewyn, B. G.; Stellmaker, M. P.; Lin, V. S.-Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 5038. (c) Vivero-Escoto, J. L.; Slowing, I. I.; Wu, C. W.; Lin, V. S. Y. *J. Am. Chem. Soc.* **2009**, *131*, 3462. (d) Torney, F.; Trewyn, B. G.; Lin, V. S. Y.; Wang, K. *Nat. Nanotechnol.* **2007**, *2*, 295. (e) Lee, J. E.; Lee, N.; Kim, H.; Kim, J.; Choi, S. H.; Kim, J. H.; Kim, T.; Song, I. C.; Park, S. P.; Moon, K. M.; Hyeon, T. *J. Am. Chem. Soc.* **2010**, *132*, 552. (f) Liu, R.; Zhang, Y.; Zhao, X.; Agarwal, A.; Muller, L. J.; Feng, P. Y. *J. Am. Chem. Soc.* **2010**, *132*, 1500. (g) Aznar, E.; Marcos, M. D.; Martinez-Manez, R.; Sancenon, F.; Soto, J.; Amoros, P.; Guillem, C. *J. Am. Chem. Soc.* **2009**, *131*, 6833. (h) Liu, R.; Liao, P.; Zhang, Z.; Hooley, R. J.; Feng, P. Y. *Chem. Mater.* **2010**, *22*, 5797.

(3) (a) Hernandez, R.; Tseng, H.-R.; Wong, J. W.; Stoddart, J. F.; Zink, J. I. *J. Am. Chem. Soc.* **2004**, *126*, 3370. (b) Nguyen, T. D.; Tseng, H.-R.; Celestre, P. C.; Flood, A. H.; Liu, Y.; Stoddart, J. F.; Zink, J. I. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 10029. (c) Nguyen, T. D.; Liu, Y.; Saha, S.; Leung, K. C.-F.; Stoddart, J. F.; Zink, J. I. *J. Am. Chem. Soc.* **2007**, *129*, 626. (d) Nguyen, T. D.; Leung, K. C.-F.; Liong, M.; Pentecost, C. D.; Stoddart, J. F.; Zink, J. I. *Org. Lett.* **2006**, *8*, 3363. (e) Angelos, S.; Yang, Y.-W.; Patel, K.; Stoddart, J. F.; Zink, J. I. *Angew. Chem., Int. Ed.* **2008**, *47*, 2222. (f) Leung, K. C.-F.; Nguyen, T. D.; Stoddart, J. F.; Zink, J. I. *Chem. Mater.* **2006**, *18*, 5919. (g) Nguyen, T. D. K.; Leung, C. F.; Liong, M.; Liu, Y.; Stoddart, J. F.; Zink, J. I. *Adv. Funct. Mater.* **2007**, *17*, 2101. (h) Patel, K.; Angelos, S.; Dichtel, W. R.; Coskun, A.; Yang, Y.-W.; Zink, J. I.; Stoddart, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 2382. (i) Lee, C.- F.; Leigh, D. A.; Pritchard, R. G.; Schultz, D.; Teat, S. J.; Timco, G. A.; Winpenny, R. E. P. *Nature* **2009**, *458*, 314. (j) Wenz, G. *J. Polym. Sci., Part A: Polym. Chem.* **2009**, *47*, 6333.

(4) (a) Schlossbauer, A.; Kecht, J.; Bein, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 3092. (b) Climent, E.; Bernardos, A.; Martinez-Manez, R.; Maquieira, A.; Marcos, M. D.; Pastor-Navarro, N.; Puchades, R.; Sancenon, F.; Soto, J.; Amoros, P. *J. Am. Chem. Soc.* **2009**, *131*, 14075. (c) Bernardos, A.; Aznar, E.; Marcos, M. D.; Martinez-Manez, R.; Sancenon, F.; Soto, J.; Barat, J. M.; Amoros, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 5884.

(5) (a) Fu, Q.; Rao, G. V. R.; Ista, L. K.; Wu, Y.; Andrzejewski, B. P.; Sklar, L. A.; Ward, T. L.; Lopez, G. P. *Adv. Mater.* **2003**, *15*, 1262. (b)

You, Y. Z.; Kalebaila, K. K.; Brock, S. L.; Oupicky, D. *Chem. Mater.* **2008**, *20*, 3354.

(6) Hong, C.-Y.; Li, X.; Pan, C.-Y. *J. Mater. Chem.* **2009**, *19*, 5155.

(7) Sun, J.-T.; Hong, C.-Y.; Pan, C.-Y. *J. Phys. Chem. C* **2010**, *114*, 12481.

(8) (a) Liu, R.; Zhao, X.; Wu, T.; Feng, P. Y. *J. Am. Chem. Soc.* **2008**, *130*, 14418. (b) Liu, R.; Zhang, Y.; Feng, P. Y. *J. Am. Chem. Soc.* **2009**, *131*, 15128.

(9) Tam, T. K.; Pita, M.; Trotsenko, O.; Motornov, M.; Tokarev, I.; Halamek, J.; Minko, S.; Katz, E. *Langmuir* **2010**, *26*, 4506.

(10) Motornov, M.; Sheparovych, R.; Lupitskyy, R.; MacWilliams, E.; Minko, S. *J. Colloid Interface Sci.* **2007**, *310*, 481.

(11) Yang, Q.; Wang, S.; Fan, P.; Wang, L.; Di, Y.; Lin, K.; Xiao, F.-S. *Chem. Mater.* **2005**, *17*, 5999.

(12) Kosmilski, M. *J. Colloid Interface Sci.* **2004**, *275*, 214.

(13) (a) Pinkrah, V. T.; Snowden, M. J.; Mitchell, J. C.; Seidel, J.; Chowdhry, B. Z.; Fern, G. R. *Langmuir* **2003**, *19*, 585. (b) Kuang, M.; Wang, D. Y.; Bao, H. B.; Gao, M. Y.; Möhwald, H.; Jiang, M. *Adv. Mater.* **2005**, *17*, 267.