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Switchable Bifunctional Stimuli-Triggered Poly-*N*-Isopropylacrylamide/DNA Hydrogels**

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Abstract: *DNA-tethered poly-N-isopropylacrylamide copolymer chains, pNIPAM, that include nucleic acid tethers have been synthesized. They are capable of inducing pH-stimulated crosslinking of the chains by i-motif structures or to be bridged by Ag^+ ions to form duplexes. The solutions of pNIPAM chains undergo crosslinking at pH 5.2 or in the presence of Ag^+ ions to form hydrogels. The hydrogels reveal switchable hydrogel-to-solution transitions by the reversible crosslinking of the chains at pH 5.2 and the separation of the crosslinking units at pH 7.5, or by the Ag^+ ion-stimulated crosslinking of the chains and the reverse dissolution of the hydrogel by the cysteamine-induced elimination of the Ag^+ ions. The DNA-crosslinked hydrogels are thermosensitive and undergo reversible temperature-controlled hydrogel-to-solid transitions. The solid pNIPAM matrices are protected against the OH^- or cysteamine-stimulated dissociation to the respective polymer solutions.*

Stimuli-responsive polymers undergoing reversible and switchable transitions between solution–hydrogel phases or hydrogel–solid phases attract growing interest in materials science.[1] Different environmental triggers, such as pH,[2] redox reactions,[3] chemical agents,[4] supramolecular recognition events,[5] light,[6] electrical,[7] or thermal[8] stimuli have been implemented to control reversible phase transitions of polymers. Different applications of stimuli-switchable polymers were suggested, including controlled drug delivery,[9] tissue engineering,[10] micromechanical systems acting as actuators and artificial muscles,[11] sensors and biosensors,[12] "smart" coating materials,[13] and more. Temperature-responsive polymers are a major class of stimuli-switchable polymers undergoing reversible temperature-controlled sol-to-gel or gel-to-solid phase transitions.[14] The most extensively studied thermosensitive polymer is the covalently crosslinked poly(*N*-isopropylacrylamide) (pNIPAM)[15] that undergoes a reversible gel-to-solid transition at ca. 32 °C. The transition temperature of pNIPAM was controlled by the introduction of groups of enhanced hydrophobicity[16] or the incorporation of ions, such as Cu^{2+}, Ag^+, or Hg^{2+}.[17] Particularly interesting are thermoresponsive polymers exhibiting dual triggering features. For example, the incorporation of photoisomerizable units, such as azobenzenes[18] or nitrospiropyran,[19] into pNIPAM allowed the photochemical switching of the thermoresponsive properties of pNIPAM. Different applications of thermosensitive polymers and of dual-triggered thermoresponsive polymers were suggested, including their use for controlled drug release, their application as thermometers, the use of thermosensitive polymer/metal nanoparticles for switchable catalysis,[17] and the application of photoactive pNIPAM for information storage and the inscription of patterns.[20]

Stimuli-switchable biopolymers, particularly DNA, that undergo solution/hydrogel transitions have been extensively studied in recent years.[21] Two general strategies to design switchable DNA hydrogels were reported: By one method, multi-valent branched DNA nanostructures were crosslinked by stimuli-responsive nucleic acids.[22] The second approach has involved the tethering of nucleic acids to hydrophilic polymer chains, for example polyacrylamide chains, and the use of the nucleic acids as functional components to crosslink the chains into hydrogel structures.[23] Different triggers, such as strand displacement,[24] K^+-stabilized G-quadruplexes/crown ether,[25] or metal ion/ligand[26] (Ag^+/cysteamine), were used for the cyclic reversible transitions between DNA-based polymer hydrogels and DNA–polymer solutions. Also, the catalytic one-cycle dissociation of DNA-based hydrogels by the cleavage of the bridging units, using enzymes or DNAzymes as catalysts, was demonstrated.[27] Different applications of switchable DNA hydrogels were suggested, including sensing,[28] removal of hazardous metal ions,[29] for example Hg^{2+} ions, inscription of structural information,[30] switchable fluorescence properties,[31] and switchable DNAzyme functionalities.[25] Despite the extensive efforts to develop new functional materials by grafting oligonucleotides to organic polymers,[32] it is interesting to note that the conjugation of DNA to pNIPAM is basically unexplored, and that the use of DNA/pNIPAM hybrid as a dual stimuli-responsive material is unknown. In the present study, we report on the synthesis of nucleic acid-functionalized pNIPAM polymers and on the cyclic and reversible dual-stimuli thermoresponsive hydrogel-to-solid transitions of the systems. We use pH or metal-ion/ligands as co-triggers for the phase transitions of the polymers. We also show that the

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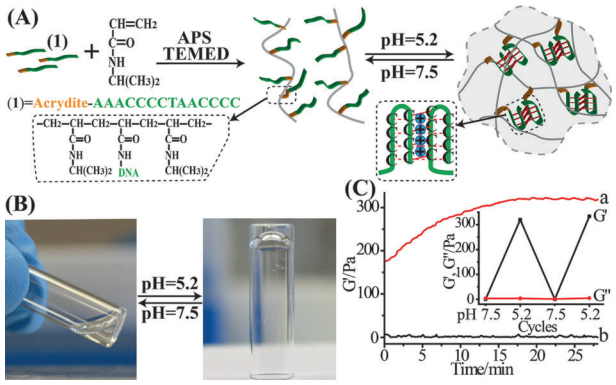

Figure 1. A) Synthesis of the DNA **1**-modified pNIPAM copolymer and its pH-switchable formation and dissociation of the i-motif-crosslinked hydrogel. B) Images of the pH-stimulated pNIPAM copolymer in the solution (left) and hydrogel (right) states. C) Rheology studies following the time-dependent storage modules, G′, upon: a) The formation of the hydrogel at pH 5.2; b) The treatment of the hydrogel at pH 7.5. Inset: Cyclic switchable changes of the storage modules, G′, and of the loss modulus, G″, upon the treatment of the pNIPAM copolymer at pH 7.5 and pH 5.2.

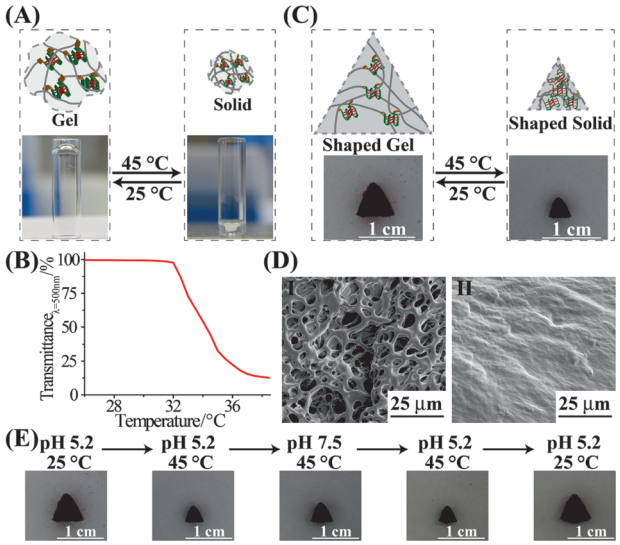

Figure 2. A) Thermally induced hydrogel-to-solid reversible transition of the i-motif-crosslinked pNIPAM copolymer. B) Transmittance changes upon the temperature-induced transition of the pNIPAM/DNA (**1**) hydrogel to the solid state. C) Cyclic reversible thermally induced transitions of the triangle-shaped hydrogel-to-solid-state structures. D) SEM images of the Au/Pd coated pNIPAM structures: (I) The hydrogel pNIPAM; (II) The solid pNIPAM structure generated upon heating the hydrogel. E) Sequential subjecting of the triangle-shaped pNIPAM hydrogel to temperature and pH triggers. Results demonstrate that the solid structure formed by heating the i-motif-crosslinked pNIPAM hydrogel to 45 °C is not dissociated to the pNIPAM solution upon treatment at pH 7.5. Au NPs were incorporated into the hydrogel to record the images.

oligonucleotide-functionalized polymers preserve the structures of the matrices, thus allowing the cyclic switching between structures of geometrical similarities.

Figure 1 A depicts the synthesis of the pH-triggered pNIPAM copolymer. The nucleic acid **1**-functionalized acrylamide monomer was polymerized in the presence of the *N*-isopropylacrylamide (NIPAM) monomer to form the hybrid copolymer consisting of pNIPAM and the tethered nucleic acids **1**. The oligonucleotide tethers include the C-rich sequences that can self-assemble at an acidic pH (pH 5.2) into the i-motif structure.[33] At slightly basic conditions, pH 7.5, the i-motif structure is unstable, and the tethers exist in a random-coil configuration, resulting in the DNA/pNIPAM solution. Figure 1 B depicts the images of the cyclic pH-stimulated solution to hydrogel transitions of the **1**-functionalized pNIPAM (the ratio of **1** to NIPAM units corresponds to 1:228. For the determination of the ratio, see the Supporting Information, Figure S1). At room temperature and at pH 7.5, the **1**-modified pNIPAM exists as a polymer solution. Acidification of the polymer solution (pH 5.2) results in the formation of the polymer gel. The pH-stimulated solution-to-hydrogel transitions are fully reversible. Control experiments revealed that a random nucleic acid sequence-modified pNIPAM (a sequence lacking the ability to form the i-motif structure) does not lead to the formation of a hydrogel. Figure 1 C shows the rheological characterization of the pH-stimulated transition of the **1**-functionalized-pNIPAM. The high storage modulus ($G' \approx 320$ Pa) of the polymer at pH 5.2 and the low loss modulus ($G'' \approx 5$ Pa) indicate that the polymer is indeed in a hydrogel phase. Also, Figure 1 C (inset) shows the cyclic switchable changes of the storage modulus values upon forming the hydrogel at pH 5.2 and the transition of the hydrogel to the polymer solution at pH 7.5. Furthermore, the hydrogel stiffness is controlled by the loading of the pNIPAM copolymer with the pH-sensitive nucleic acid tethers (Supporting Information, Figure S2). As the loading is lowered, the stiffness of the hydrogel decreases, as evident by lower values of the storage modulus of the polymers.

Figure 2 A depicts the temperature-controlled effects on the i-motif-crosslinked hydrogel. While at room temperature (25 °C; pH 5.2), the polymer exists as a hydrogel, heating the hydrogel to 45 °C results in the shrinking of the polymer into a small-volume collapsed solid structure, implying that the water encapsulated in the hydrogel is expelled from the polymer structure. The hydrogel-to-solid transitions of the hydrogel are fully reversible, and cooling the system to 25 °C regenerates the swollen hydrogel structure. Control experiments revealed that the **1**-modified pNIPAM did not shrink at pH 7.5 into the solid phase upon heating to 45 °C. These results imply that the i-motif crosslinking units, and the NIPAM units, act cooperatively in generating the solid phase of the polymer. Figure 2 B depicts the transmittance change upon heating the **1**-modified pNIPAM. A clear drop in the transmittance is observed at about 33 °C, suggesting that this is the gel-to-solid transition temperature. Figure 2 C depicts the shape-retaining properties of the i-motif-crosslinked pNIPAM. In this experiment, the i-motif-crosslinked hydrogel was prepared in a Teflon mold in a triangle shape. The hydrogel triangle was then extracted from the mold, and subjected to heating/cooling cycles. Heating the room temperature-generated triangle structure to 45 °C results in the small triangle structure, and cooling the system restores the swollen

hydrogel triangle structure. The system is fully reversible, and cyclic heating the hydrogel triangle to 45 °C and back to room temperature transforms the structure between small and expanded shapes. The thermosensitive triangle polymer shape could be cycled between the swollen hydrogel structure and the solid state for five cycles with no noticeable changes in the geometric features of the shapes. Figure 2 D depicts the SEM images corresponding to the freeze-dried i-motif-crosslinked pNIPAM hydrogel, generated at 25 °C (panel I), and of the solid polymer structure, generated at 45 °C (panel II). While the hydrogel matrix reveals a porous material (pores in the range of 1.7 to 6.6 μm), the solid polymer shows a non-porous, smooth structure. Figure 2 E shows, however, an interesting phenomenon whereby the shaped solid i-motif pNIPAM structure at 45 °C is resistant to pH changes and retains to triangle structure even at pH 7.5. In this system, the i-motif pNIPAM hydrogel triangle structure, generated at pH 5.2 and 25 °C, is subjected to an increase in the temperature to 45 °C. As expected, the shaped hydrogel shrinks owing to its solidification. Treatment of the solid triangle-shaped structure at 45 °C and in pH 7.5 buffer solution does not affect the shape of the structure for a time interval of at least four hours. This implies that the i-motif crosslinking units are not dissociated by the exterior pH, suggesting that the solid polymer phase blocks the penetration of OH^- ions into the polymer matrix. The subsequent treatment of the shrunken triangle structure with a solution pH 5.2 and the subsequent cooling of the system to 25 °C restores the expanded shaped hydrogel. In turn, cooling the protected small hydrogel structure at pH 7.5 to 25 °C dissolves the matrix and yields a solution of (**1**)-pNIPAM.

A further approach to design switchable dual-triggered DNA/pNIPAM thermosensitive polymers has involved the metal-assisted crosslinking of duplex bridging strands using Ag^+-ions and the separation of the bridging units by the cysteamine-stimulated elimination of the Ag^+ ions of the duplexes. Cytosine–cytosine mismatches in duplex DNA structures can be bridged by C-Ag^+-C complexes that cooperatively stabilize the double-stranded structures.[34] Accordingly, the Ag^+/cysteamine-triggered pNIPAM was designed as outlined in Figure 3 A. Copolymer chains consisting of the NIPAM monomers and the **2**-modified acrylamide units were prepared. The oligonucleotide tethers **2** exhibit self-complementary and C–C mismatches. The ratio between the NIPAM units and the **2**-acrylamide units corresponded to 420:1 (for the determination of the loading see the Supporting Information, Figure S3). The **2**-functionalized pNIPAM chains are fully soluble in water, 25 °C, pH 7.5, since the complementarity between the units **2** is insufficient to form stable duplex bridges. In the presence of Ag^+ ions, the C-Ag^+-C bridges co-stabilize the duplex formation between the oligonucleotide tethers, resulting in the crosslinking of polymer chains and the formation of the hydrogel. Treatment of the hydrogel with cysteamine eliminates the Ag^+ from the bridging units, leading to the separation of the hydrogel and to the formation of the polymer solution. Figure 3 B depicts the images of the switchable Ag^+-ion-stimulated formation of the hydrogel, and the reverse separation of the hydrogel, in the presence of

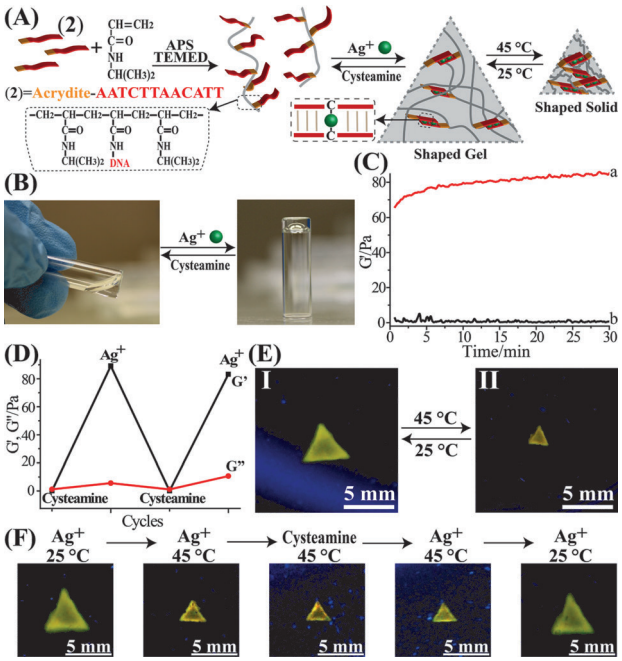

Figure 3. A) Synthesis of a pNIPAM copolymer consisting of the pNIPAM monomer and of **2**, and the Ag^+-assisted crosslinking of the chains to a hydrogel. The hydrogel undergoes switchable separation and reformation upon treatment with cysteamine and Ag^+ ions, respectively. The Ag^+-crosslinked hydrogel undergoes cyclic thermal transitions between the hydrogel and solid states. B) Images corresponding to the Ag^+-stimulated transition of the pNIPAM copolymer solution to the hydrogel and the reverse dissolution of the hydrogel in the presence of cysteamine. C) The storage modulus *G′* corresponding to: a) the Ag^+-crosslinked pNIPAM; b) The pNIPAM copolymer solution in the absence of Ag^+-ions. D) Cyclic changes of the storage modulus, *G′*, and loss modulus, *G″*, upon treatment of the system with Ag^+ ions and cysteamine as triggers. E) Temperature-induced transitions of the Ag^+-crosslinked triangle-shaped hydrogel to solid structures and back. F) Sequential subjecting of the triangle-shaped pNIPAM/(**2**) hydrogel to temperature and Ag^+/cysteamine triggers. The results demonstrate that the solid structure formed by heating the Ag^+ ions crosslinked pNIPAM/(**2**) hydrogel to 45 °C is not dissociated to the pNIPAM/(**2**) solution upon the treatment with cysteamine. The hydrogel is functionalized with SYBR gold to record the images.

cysteamine. The Ag^+-stimulated hydrogelation of the polymer chains and the reverse cysteamine-induced dissolution of the hydrogel are rapid processes and proceed within 10 min. We observed, however, that the Ag^+-stimulated hydrogelation of the chains is slightly slower than the hydrogel dissolution by cysteamine. This might be explained by the fact that the hydrogel core generated upon addition of Ag^+ ions retards the diffusion of Ag^+ to the polymer solution phase. In contrast, addition of cysteamine yields a liquid solution pool that facilitates the diffusion of cysteamine to the surrounding hydrogel. The Ag^+-generated hydrogel was rheologically characterized (Figure 3 C,D). The Ag^+-ion crosslinked hydrogel reveals a storage modulus value of about 85 Pa, while the loss modulus of the system corresponding to about 4 Pa, consistent with a hydrogel structure of the system. By the cyclic treatment of the Ag^+-crosslinked hydrogel with cysteamine and Ag^+ ions, the storage modulus

of the system was switched between low and high values, respectively (Figure 3D), consistent with the formation of a polymer solution and hydrogel system, respectively. Heating of the Ag^+-bridged hydrogel led to the transition of the hydrogel into a solid. The gel-to-solid transition temperature was evaluated to be about 32.5 °C. Cooling the solid polymer to 25 °C regenerated the hydrogel Ag^+-crosslinked polymer. Figure 3E depicts the reversible thermally induced shape-controlled transitions of the hydrogel to the solid phase and back. The Ag^+-**2**-crosslinked pNIPAM hydrogel was generated in the Teflon mold, and the image of the extracted hydrogel at 25 °C is shown in Figure 3E, panel I. Heating of the hydrogel to 45 °C yields the compressed, geometrically similar, triangle structure corresponding to the solid polymer (panel II). The further cooling of the solid polymer structure restores the triangle hydrogel. The thermosensitive triangle-shaped Ag^+-crosslinked (**2**)-pNIPAM exhibits structural transition stabilities. Upon heating the Ag^+-crosslinked hydrogel to 45 °C and the subsequent cooling of the polymer to 25 °C, the triangle shape could be cycled between the compressed solid state and the swollen hydrogel state for five cycles, with no noticeable distortion of the shape. Interestingly, the solid Ag^+-crosslinked pNIPAM copolymer is resistant to dissociation to the solution phase upon the addition of cysteamine (Figure 3F). That is, the solid structure of the copolymer prohibits the penetration of cysteamine to the polymer structure, and thus, the removal of the crosslinking Ag^+ ions is avoided. For further characterization of the thermosensitive Ag^+-ion-crosslinked pNIPAM system, see the Supporting Information, Figure S4 (effect of the nucleic acid loading on the systems of copolymer), Figure S5 (evaluation of the phase transition temperature), and Figure S6 (SEM images of the porous pNIPAM hydrogel and solid after heating).

In conclusion, the present study has introduced oligonucleotide-modified pNIPAM as dual-stimuli responsive polymers that undergo cyclic transitions between polymer solution-hydrogel-solid states. We have demonstrated that pH changes or Ag^+-ions/cysteamine effect the cyclic transitions between polymer solutions and the hydrogel states. The resulting hydrogels undergo thermally stimulated cyclic and reversible hydrogel-to-solid-phase transitions. We have further demonstrated that shaped structures of the hydrogels undergo thermally controlled reversible hydrogel/solid transitions that preserve geometrical similarities of the polymer shapes. Such oligonucleotide-modified pNIPAM matrices could find important applications for sensing, controlled drug release, and the inscription of information.

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[1] a) K. Y. Lee, D. J. Mooney, *Chem. Rev.* **2001**, *101*, 1869 – 1879; b) N. A. Peppas, J. Z. Hilt, A. Khademhosseini, R. Langer, *Adv. Mater.* **2006**, *18*, 1345 – 1360; c) M. A. C. Stuart, W. T. S. Huck, J. Genzer, M. Müller, C. Ober, M. Stamm, G. B. Suhorukov, I. Szleifer, V. V. Tsukruk, M. Urban, F. Winnik, S. Zauscher, I. Luzinov, S. Minko, *Nat. Mater.* **2010**, *9*, 101 – 113; d) F. Liu, M. W. Urban, *Prog. Polym. Sci.* **2009**, *35*, 3 – 23.

[2] a) S. Dai, P. Ravi, K. C. Tam, *Soft Matter* **2008**, *4*, 435 – 449; b) S. R. Haines, R. G. Harrison, *Chem. Commun.* **2002**, 2846 – 2847.

[3] A. Akhoury, L. Bromberg, T. L. Hatton, *ACS Appl. Mater. Interfaces* **2011**, *3*, 1167 – 1174.

[4] Y. Lvov, A. A. Antipov, A. Mamedov, H. Möhwald, G. B. Sukhorukov, *Nano Lett.* **2001**, *1*, 125 – 128.

[5] a) K. Murata, M. Aoki, T. Nishi, A. Ikeda, S. Shinkai, *J. Chem. Soc. Chem. Commun.* **1991**, 1715 – 1718; b) J. B. Beck, S. J. Rowan, *J. Am. Chem. Soc.* **2003**, *125*, 13922 – 13923; c) J. Yuan, D. Wen, N. Gaponik, A. Eychmüller, *Angew. Chem.* **2013**, *125*, 1010 – 1013; *Angew. Chem. Int. Ed.* **2013**, *52*, 976 – 979.

[6] a) Y. Zhao, *J. Mater. Chem.* **2009**, *19*, 4887 – 4895; b) Y. Zhao, *Macromolecules* **2012**, *45*, 3647 – 3657.

[7] Q. Yan, J. Yuan, Z. Cai, Y. Xin, Y. Kang, Y. Yin, *J. Am. Chem. Soc.* **2010**, *132*, 9268 – 9270.

[8] K. Kuroiwa, T. Shibata, A. Takada, N. Nemoto, N. Kimizuka, *J. Am. Chem. Soc.* **2004**, *126*, 2016 – 2021.

[9] a) M. E. Byrne, K. Park, N. A. Peppas, *Adv. Drug Delivery Rev.* **2002**, *54*, 149 – 161; b) J. Z. Hilt, M. E. Byrne, *Adv. Drug Delivery Rev.* **2004**, *56*, 1599 – 1620; c) A. S. Hoffman, *J. Controlled Release* **2008**, *132*, 153 – 163.

[10] a) J. A. Rowley, G. Madlambayan, D. J. Mooney, *Biomaterials* **1999**, *20*, 45 – 53; b) K. Y. Lee, D. J. Mooney, *Chem. Rev.* **2001**, *101*, 1869 – 1879.

[11] a) D. J. Beebe, J. S. Moore, J. M. Bauer, Q. Yu, R. H. Liu, C. Devadoss, B. H. Jo, *Nature* **2000**, *404*, 588 – 590; b) J. H. Holtz, S. A. Asher, *Nature* **1997**, *389*, 829 – 832.

[12] a) J. N. Anker, W. P. Hall, O. Lyandres, N. C. Shah, J. Zhao, R. P. Van Duyne, *Nat. Mater.* **2008**, *7*, 442 – 453; b) I. Tokarev, S. Minko, *Soft Matter* **2009**, *5*, 511 – 524.

[13] a) P. M. Mendes, *Chem. Soc. Rev.* **2008**, *37*, 2512 – 2529; b) I. Luzinov, S. Minko, V. V. Tsukruk, *Soft Matter* **2008**, *4*, 714 – 725; c) M. Motornov, S. Minko, K.-J. Eichhorn, M. Nitschke, F. Simon, M. Stamm, *Langmuir* **2003**, *19*, 8077 – 8085; d) Z. S. Liu, P. Calvert, *Adv. Mater.* **2000**, *12*, 288 – 291.

[14] a) F. D. Jochum, P. Theato, *Chem. Soc. Rev.* **2013**, *42*, 7468 – 7483; b) B. Jeong, S. W. Kim, Y. H. Bae, *Adv. Drug Delivery Rev.* **2012**, *64*, 154 – 162.

[15] H. G. Schild, *Prog. Polym. Sci.* **1992**, *17*, 163 – 249.

[16] a) H. G. Schild, D. A. Tirrell, *Langmuir* **1991**, *7*, 665 – 671; b) H. G. Schild, D. A. Tirrell, *Polym. Prepr. Am. Chem. Soc. Div. Polym. Chem.* **1989**, *30*, 350 – 351.

[17] M. Riskin, R. Tel-Vered, I. Willner, *Adv. Funct. Mater.* **2009**, *19*, 2474 – 2480.

[18] a) Y. Maeda, T. Nakamura, I. Ikeda, *Macromolecules* **2001**, *34*, 1391 – 1399; b) A. Desponds, R. Freitag, *Langmuir* **2003**, *19*, 6261 – 6270; c) T. Ueki, Y. Nakamura, A. Yamaguchi, K. Niitsuma, T. P. Lodge, M. Watanabe, *Macromolecules* **2011**, *44*, 6908 – 6914.

[19] Y. Shiraishi, R. Miyamoto, T. Hirai, *Org. Lett.* **2009**, *11*, 1571 – 1574.

[20] S. Wang, M.-S. Choi, S.-H. Kim, *J. Photochem. Photobiol. A* **2008**, *198*, 150 – 155.

[21] a) Y. H. Roh, R. C. H. Ruiz, S. Peng, J. B. Lee, D. Luo, *Chem. Soc. Rev.* **2011**, *40*, 5730 – 5744; b) J. Liu, *Soft Matter* **2011**, *7*, 6757 – 6767.

[22] a) S. H. Um, J. B. Lee, N. Park, S. Y. Kwon, C. C. Umbach, D. Luo, *Nat. Mater.* **2006**, *5*, 797 – 801; b) E. Cheng, Y. Xing, P. Chen, Y. Yang, Y. Sun, D. Zhou, L. Xu, Q. Fan, D. Liu, *Angew. Chem.* **2009**, *121*, 7796 – 7799; *Angew. Chem. Int. Ed.* **2009**, *48*, 7660 – 7663.

[23] a) B. Wei, I. Cheng, K. Q. Luo, Y. Mi, *Angew. Chem.* **2008**, *120*, 337 – 339; *Angew. Chem. Int. Ed.* **2008**, *47*, 331 – 333; b) H. H. Yang, H. Liu, H. Kang, W. Tan, *J. Am. Chem. Soc.* **2008**, *130*, 6320 – 6321.
[24] T. Liedl, H. Dietz, B. Yurke, F. C. Simmel, *Small* **2007**, *3*, 1688 – 1693.
[25] C. H. Lu, X. J. Qi, R. Orbach, H. H. Yang, I. Mironi-Harpaz, D. Seliktar, I. Willner, *Nano Lett.* **2013**, *13*, 1298 – 1302.
[26] W. Guo, X. J. Qi, R. Orbach, C. H. Lu, L. Freage, I. Mironi-Harpaz, D. Seliktar, H. H. Yang, I. Willner, *Chem. Commun.* **2014**, *50*, 4065 – 4068.
[27] a) Y. Xing, E. Cheng, Y. Yang, P. Chen, T. Zhang, Y. Sun, Z. Yang, D. Liu, *Adv. Mater.* **2011**, *23*, 1117 – 1121; b) H. Lin, Y. Zou, Y. Huang, J. Chen, W. Y. Zhang, Z. Zhuang, G. Jenkins, C. J. Yang, *Chem. Commun.* **2011**, *47*, 9312 – 9314.
[28] K. A. Joseph, N. Dave, J. Liu, *ACS Appl. Mater. Interfaces* **2011**, *3*, 733 – 739.
[29] N. Dave, M. Y. Chan, P. J. Huang, B. D. Smith, J. Liu, *J. Am. Chem. Soc.* **2010**, *132*, 12668 – 12673.
[30] J. B. Lee, S. Peng, D. Yang, Y. H. Roh, H. Funabashi, N. Park, E. J. Rice, L. Chen, R. Long, M. Wu, D. Luo, *Nat. Nanotechnol.* **2012**, *7*, 816 – 820.
[31] W. Guo, R. Orbach, I. Mironi-Harpaz, D. Seliktar, I. Willner, *Small* **2013**, *9*, 3748 – 3752.
[32] M. Kwak, A. Herrmann, *Angew. Chem.* **2010**, *122*, 8754 – 8768; *Angew. Chem. Int. Ed.* **2010**, *49*, 8574 – 8587.
[33] a) K. Gehring, J. L. Leroy, M. Guéron, *Nature* **1993**, *363*, 561 – 565; b) F. Xia, W. Guo, Y. Mao, X. Hou, J. Xue, H. Xia, L. Wang, Y. Song, H. Ji, Q. Ouyang, Y. Wang, L. Jiang, *J. Am. Chem. Soc.* **2008**, *130*, 8345 – 8350.
[34] A. Ono, S. Cao, H. Togashi, M. Tashiro, T. Fujimoto, T. Machinami, S. Oda, Y. Miyake, I. Okamoto, Y. Tanaka, *Chem. Commun.* **2008**, 4825 – 4827.

