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Dynamic Materials

Autonomic Self-Healing of Hydrogel Thin Films**

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Self-healing materials have the ability repair themselves following damage. Over the past few decades, there has been a growing interest in materials that can self-heal, as this property can increase a material's lifetime, reduce replacement costs, and improve product safety. Self-healing systems can be made from a variety of materials, but polymers have been extensively explored because of their chemical and mechanical tunability, and the ability to create dynamic materials.[1–4] Although the vast majority of these previous studies have explored healing processes in robust polymeric structures such as epoxy coatings[5–7] and elastomers,[8] more delicate architectures such as hydrogel thin films have not yet been studied as self-healing materials that can heal induced mechanical damage. Herein, we report autonomic self-healing polymeric thin films assembled from colloidal hydrogel building blocks. By employing a layer-by-layer polyelectrolyte approach in the fabrication, we have developed a material, which, upon exposure to water, undergoes rapid (on a timescale of seconds) healing of micrometer-sized defects that span the entire coated area (1 cm^2), with no apparent remnant damage even at submicron length scales. The self-healing properties displayed by these coatings enable the use of hydrated polymer films in applications where rough (e.g., surgical) handling and transient damage are inevitable, such as in biomedical implants.

Most materials do not have the inherent ability to heal themselves, typically because their building blocks are organized into rigid architectures and therefore cannot migrate across defects that are longer than the molecular length scale, or because the molecular components are not chemically labile enough to reform bonds after rupture. In fact, most materials suffer from both these problems. However, several research groups have developed approaches to solve these issues. Materials that undergo reversible reactions between functional groups or weak interactions within the polymer matrix can successfully be mended following the introduction of a defect.[6,8,9] This approach is limited to particular chemical reactions and often the residual "dangling chains" will interact with other chains on a single side of the gap, as opposed to cross-gap interaction, thus preventing healing if the material is not mechanically reconnected soon after cutting. Another approach involves heating the polymer above its glass transition temperature (T_g), thereby increasing the mobility of the chains and causing rearrangement and molecular interdiffusion to promote "crack healing".[10–12] The obvious limitation to this approach is the need for the external application of heat, therefore truly autonomous healing is not possible. Other demonstrations involve filling a void by the release of healing agents or inhibitors into cracks,[5,7,13,14] or by an induced phase separation of nanoparticles towards damaged areas.[15] However, only limited numbers of the embedded reservoirs or nanoparticles are incorporated, and therefore it is unlikely that such materials could continue to heal after recurrent damage in the same area.

Herein we describe a "self-healing" hydrogel film that can withstand repeated deformation and quickly recover its original structure when solvated with water. Hydrogels (cross-linked polymeric networks swollen with water) have been a topic of growing interest over the past twenty years because of their unique properties and the wide variety of applications in which they can be exploited.[16–18] The films described below are fabricated by layer-by-layer (LbL) polyelectrolyte self-assembly,[19] which has been demonstrated for a vast variety of materials,[20,21] thus offering universal utility to the method. In our approach, we employ spherical, sub-micrometer-sized hydrogel particles (microgels) as the main building block in the LbL assembly procedure to fabricate continuous, multilayered hydrogel films. We have previously demonstrated the use of microgels to fabricate 2D and 3D arrays on solid substrates by LbL assembly.[22–24] In these earlier studies, it became apparent that a cationic linear polymer was able to penetrate the microgels and strongly cross-link the anionic acidic side chains within the microgels. Subsequent addition of another microgel layer resulted in a 3D coulombically cross-linked hydrogel network. These investigations led to an understanding of how linear polyelectrolytes can render individual microgels "sticky", and also how the interplay of both strong and weak interactions impact the assembly and swelling properties of such materials.

During the course of our previous studies, observations were made that suggested dynamic microgel reorganization within the films. Although these observations were not quantitatively explored at that time, they suggested the potential for defect healing properties. Thus, to more precisely investigate the response of microgel multilayers to controlled damage, the films were deposited on an elastomeric substrate, poly(dimethylsiloxane) (PDMS), which allowed for the controlled mechanical manipulation of the substrate and its associated microgel coating. Using a chemical treatment of PDMS that renders the surface of the

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material hydrophilic,[25] functionality, to which the first layer of microgels could be covalently attached, was introduced to the substrate. The presence of surface hydroxyl groups allowed for silanization using (3-aminopropyl)trimethoxysilane (APTMS), to which acid-containing microgels adsorbed by coulombic attraction. Subsequently, the monolayer was covalently bound using a carbodiimide coupling reaction.[26] Four microgel layers were assembled using alternating layers of anionic microgels and poly(diallyldimethylammonium chloride) (PDADMAC), a cationic quaternary amine. A representative film is shown in Figure 1 a–c at different

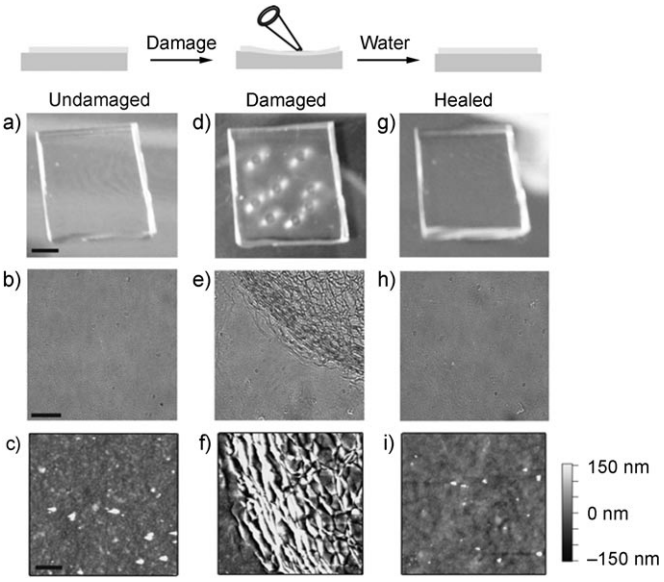

Figure 1. Visualization of damage introduced by multiple "stabs" with a 5 μL pipette tip. Images were taken by digital camera (a, d, g; scale bar = 2.5 mm), brightfield optical microscopy (b, e, h; scale bar = 20 μm), and atomic force microscopy (c, f, i; scale bar = 10 μm), before damage (a–c), after damage (d–f), and after healing by rehydration (g–i).

magnifications. Image (a) is a photograph of coated 1 mm thick PDMS on a supporting microscope coverslip, while images (b) and (c) are bright field microscopy and atomic force microscopy (AFM) images, respectively. At all magnifications, the films appear homogeneous, with the dominant roughness features (observed by AFM) arising from the microgel building blocks.

The films shown in Figure 1 were fabricated from microgels composed of *N*-isopropylacrylamide (NIPAm; 71 mol%), acrylic acid (AAc; 26 mol%), and the crosslinker poly(ethylene glycol) diacrylate ($M_w = 575$, PEGDA-575; 3.5 mol%). The microgels have a hydrodynamic radius of (277 ± 25) nm and (510 ± 31) nm at pH 3 and pH 7.4, respectively. The particle height in the dehydrated state on a glass surface was approximately 60 nm. We employed these particular microgels for these studies since they are relevant to our efforts in nonfouling biomaterials coatings. Similar microgels, when used to coat an implantable biomaterial, have been shown to dramatically reduce both protein and cellular adhesion in vitro,[27,28] and reduce leukocyte recruitment and cytokine release in vivo.[29] These previous studies illustrated the effectiveness of using nonfouling microgels as a coating for reducing the foreign body response. Such a coating can ultimately improve the performance and lifetime of implantable biomedical devices. Importantly, we now show that such coatings can likely withstand the rigors of surgical handling and should autonomously heal any defects associated with the act of implantation.

After assembly of the microgel film on PDMS, any physical contact with the coating appeared to change the film appearance dramatically. Although a razor blade is commonly used to induce damage to demonstrate self-healing, this approach was avoided to prevent irreversible damage to the PDMS. Therefore, a 5 μL pipette tip—an object with a blunt tip—was used to illustrate the macroscopic healing properties. As can be seen in Figure 1 d–f, a ring remained on the film after simply pressing the tip into the surface. The ring defect can be seen by optical microscopy and AFM, as well as by eye, and renders deep grooves and ruffled regions in the film that are a few micrometers wide. During damage, it appears that the microgels are redistributed, which is apparent by the elevated regions (high microgel density) along the edges of the cracks (low microgel density). However, addition of water to the film erases these defects without observable desorption of microgels from the film (Figure 1 g–i). In fact, the defects heal so quickly (on a timescale of seconds), that direct microscopic observation of the healing process has not yet been possible. For example, addition of water to the film necessitates manual refocusing of the optical microscope; this process takes longer than the defect healing time (see the Supporting Information for a short movie of the rapid healing process). It is important to point out that these defects do not occur on chemically treated and silanized PDMS (see the Supporting Information) alone, and are exclusively associated with the hydrogel coating. Furthermore, a high salt solution concentration (1M) and warm temperatures (50°C) do not prevent the rapid healing of these films and do not induce particle desorption (data not shown). From these results, it is apparent that microgel-based films can survive extensive disturbances from an external object, and then undergo dramatic rearrangement back to the original structure.

To interrogate how controlled mechanical stretching and bending of the material would affect the microgel coating, 1 cm × 1 cm × 1 mm (l × w × h) PDMS pieces coated with microgel multilayers were stretched by 10% in length and bent to an angle of 90 degrees. Figure 2 shows optical microscopy images of the damage that occurs during these treatments. Stretching creates parallel breaks or cracks in the film that are perpendicular to the axis of stretching, whereas bending generates a 2D network of fractures. The inset images confirm the presence of the particulate film in the damaged region; the observed defects are present in the coating and not the underlying PDMS. Again, upon addition of water, the microgel multilayers recover their original continuous structure without any evidence of breaks in the film. In Figure 3, topographical changes are shown by line profiles drawn across the entire width of the AFM images. Defects as deep as 400 nm and as wide as 4 μm occur during

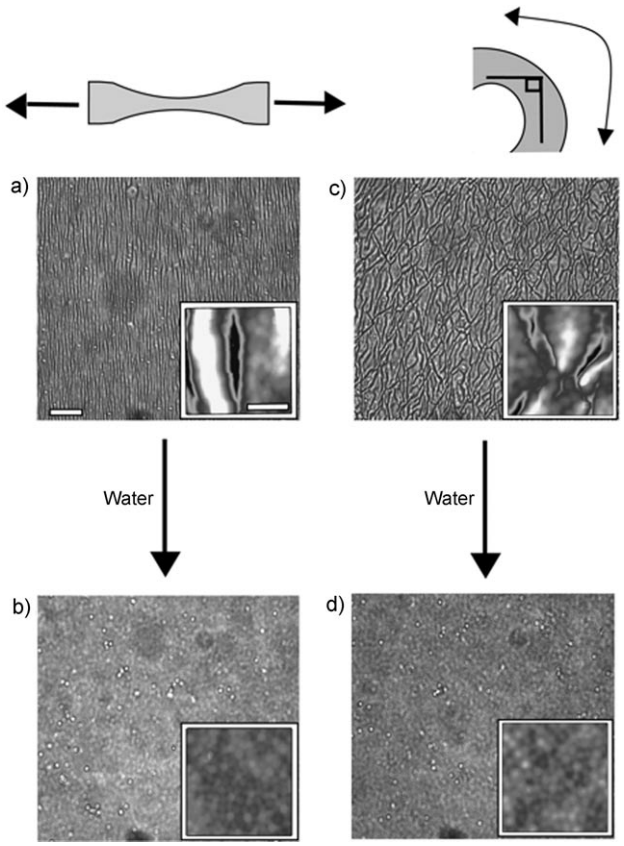

Figure 2. Film damage introduced by stretching (a) and bending (c) deformation, as observed by brightfield optical microscopy (scale bar = 10 μm). Samples are shown after deformation (a, c) and after healing (b, d). During bending of the sample (c), the microgel film is present on the outer surface. The insets show 5 μm × 5 μm AFM scans of the damaged or healed regions (scale bar = 1 μm).

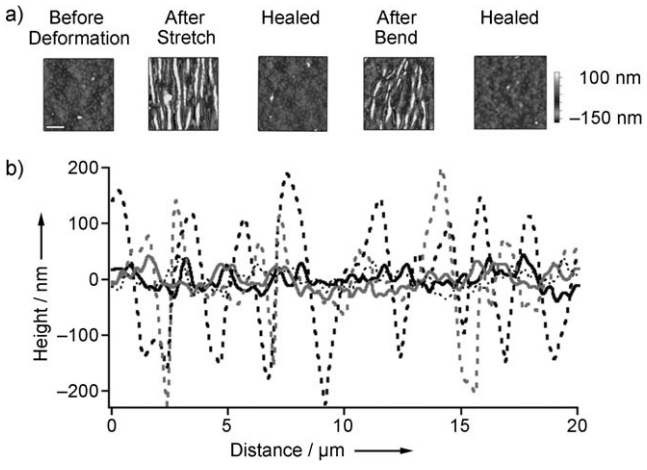

Figure 3. a) AFM scans (20 μm × 20 μm) of defects induced on the same sample before deformation, after deformation, and after healing (left to right; scale bar = 5 μm). b) AFM line profiles of each scan drawn across the entire image are shown to illustrate the reversibility of the phenomenon. Before damage (solid black line), stretched (dashed black line), water healed after stretch (solid gray line), bent (dashed gray line), and water-healed after bending (dotted black line).

mechanical manipulation. After each damage event, the microgel film completely recovers its original topography. This process can be repeated on the same sample without the underlying PDMS ever becoming exposed, that is, multiple damage/healing cycles do not result in delamination of the microgel film.

The observations illustrated above clearly show the ability of microgel-based polyelectrolyte multilayers to reorganize after damage. The origins of these phenomena likely have their roots in the forces that hold the films together at equilibrium. For example, upon mechanical deformation of the elastomeric substrate, the resultant stress is transmitted to the coating. The weak links that hold the film together are coulombic in nature, and it is likely that stress-induced folding or cracking of the film results in some rupture of these polyanion–polycation interactions. Since the polycations form both inter- and intra-microgel cross-links, the dissociation of the particles likely leaves an excess positive charge on the particles, in the form of dangling polyelectrolyte chains (net positive surface charge), or bare patches on the microgels (net negative surface charge). Therefore, the damaged film, which clearly contains regions of both high and low microgel number density, will also be heterogeneous in terms of overall charge. Resolvation permits higher polymer mobility in the film, which in turn permits a redistribution of microgels to a less energetic state associated with reformation of the polyanion–polycation interactions. We have also previously shown how soft microgel colloidal crystals can heal defects, which were induced by the incorporation of a different sized microgel, within its crystalline lattice.[30] Thus, it may be the case that the self-healing properties of the films described above also have their source in the softness of the interaction potentials between neighboring particles. Though the self-healing capability is not yet completely understood in these two-dimensional microgel structures, the defect tolerance exhibited within soft colloidal assemblies examined in this other work contributes to the awareness that microgel-based assemblies are intrinsically dynamic and highly complex with respect to their interactions.

We have clearly shown that microgel polyelectrolyte multilayers exhibit repeatable self-healing behavior upon multiple mechanical deformations. By constructing the films on an elastomeric substrate (PDMS), controlled distortion of the film is permitted, thus leading to the direct observation of autonomous film repair. These are the first illustrations of autonomous healing of micron-sized defects in hydrogel films. This process is highly relevant in the context of hydrogel-based biomaterials coatings likely to be damaged by routine surgical handling. Current efforts are aimed at understanding the fundamental parameters that give rise to the healing phenomena, as well as explorations of the generality of these observations with respect to polymer type, film assembly, and substrate properties.

Experimental Section

Microgel synthesis and characterization: Microgels were synthesized using aqueous free radical precipitation polymerization. With a total monomer concentration of 124 mM, the molar composition of micro-

gel components was *N*-isopropylacrylamide (NIPAm; 70.5%), poly(ethylene glycol) diacrylate, $M_W = 575$ (PEGDA-575, 3.5%), and acrylic acid (AAc; 26%). Sodium dodecyl sulfate (SDS; 0.17 mM) and ammonium persulfate (APS; 1 mM) were used as surfactant and initiator, respectively. NIPAm and SDS were dissolved in deionized water (99 mL) and filtered through Whatman grade 2 filter paper in a vacuum filtration system. The aqueous solution was then transferred to a three-neck round bottom flask and purged with N_2 for approximately 1 hour while the solution was heated at 70 °C. Approximately 10 min before initiation, AAc and PEGDA-575 were added to the solution in the flask. APS was dissolved in deionized water (1 mL) and added to initiate the polymerization. The reaction was allowed to proceed for 4 h at 70 °C under an atmosphere of N_2. Dynamic light scattering (DLS; Protein Solutions DynaPro DLS equipped with a temperature-controlled microsampler) was used as previously described[31,32] to measure the hydrodynamic radius of synthesized particles and determine their pH responsivity. Light scattering data was collected at an interval of 10 seconds per reading with an avalanche photodiode detector fixed at 90° relative to the incident the laser light (783.9 nm). The Dynamics Software package was used to calculate the microgel diffusion coefficient from the autocorrelation decay of the random fluctuations in scattered light intensity. The diffusion coefficient of the microgels was then used to calculate the hydrodynamic radius of the particles using the Stokes–Einstein equation. Phosphate buffer (pH 7.4) and formate buffer (pH 3) were used as the dispersion medium for the measurement. ^{1}H NMR was used to verify the incorporation of PEG575 cross-linker using D_2O as the solvent.

Poly(dimethylsiloxane) (PDMS) preparation and surface modification: PDMS (Sylgard 184 purchased from Dow Corning) was prepared by mixing a 1:10 weight ratio of curing agent and elastomeric base. After sufficient mixing in a plastic petri dish, the PDMS was covered and placed in a vacuum chamber for approximately 15 min to remove air bubbles. The material was then allowed to cure in a 50 °C oven for 24 h. The PDMS was then cut into 1 cm × 1 cm squares 1 mm in thickness using a razor blade. The squares were washed in hexane until the PDMS squares stopped swelling (approximately 2 h), to ensure the removal of any uncured material. The PDMS pieces were removed from the hexane and placed in a 50 °C vacuum oven overnight to remove residual solvent. The PDMS pieces were rinsed with ethanol and deionized water, and then allowed to equilibrate in water for 1 hour. To introduce hydroxyl groups to the surface, hydrochloric acid was added to make a 1.2 M aqueous solution, and the PDMS was incubated under these conditions overnight. Afterwards, the pieces were rinsed three times with copious amounts of water. The PDMS pieces were then rinsed with absolute ethanol, equilibrated for 30 min in fresh absolute ethanol, and then APTMS was added to make the final APTMS concentration 1% by volume. Silanization of the PDMS surfaces was allowed to proceed for 2 h. Amine-functionalized PDMS could be stored up to one week in absolute ethanol before use.

Microgel film deposition: After functionalization, the PDMS pieces were rinsed with ethanol and deionized water, and then blown dry with nitrogen. Pieces were individually placed at the bottom of a 24-well plate and 20 mM phosphate buffered saline (PBS) (pH 7.4; 100 mM ionic strength) was immediately added. The PDMS was allowed to equilibrate for 30 min, and the buffer was then replaced with a 0.1 mg mL^{-1} solution of microgels in the same PBS. Deposition was performed using a centrifugation method where centrifugal force is used to quickly deposit microgels onto a substrate. Using centrifugal deposition, the well plates were placed across a counterweighted well plate in an Eppendorf 5804R centrifuge equipped with a plate-holding rotor. Films were centrifugally deposited at a maximum rotor speed of 2250 *g* for 5 min. After deposition, the monolayers were covalently attached to the amine-functionalized PDMS by activating the acids on the particles with *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (EDC) followed by active ester formation with *N*-hydroxysuccinimide (NHS).[26] A solution containing EDC (2 mM) and NHS (5 mM) was prepared in 100 mM 2-(*N*-morpholino)ethanesulfonic acid (MES) buffer (pH 5.5) and allowed to react with the microgel monolayer for 2 h at room temperature. The films were then rinsed with water to remove excess reagents. We have previously demonstrated the use of microgels in the fabrication of multilayered thin films.[22,33–35] To add an additional layer, a solution of poly(diallyldimethylammonium chloride (PDADMAC, 0.14 monoM (molar concentration of monomer)) was added to the film and allowed to adsorb to the microgel film for 30 min. The films were then washed five times with deionized water. Another layer of microgels was then added to the well and centrifuged onto the surface, as described above. This process was repeated until four microgel layers were deposited and the top layer consisted of microgels.

Film characterization: Films were characterized using three imaging methods. A FujiFilm FinePix J20 camera with a 10 megapixel CCD chip was used to capture unmagnified images. Brightfield optical microscopy at 40× magnification was also performed on an Olympus IX-70 inverted microscope equipped with a Cooke Corporation PixelFly black and white CCD camera. Microgel films were also imaged using an Asylum Research MFP-3D AFM (Santa Barbara, CA). Imaging was performed and processed using the MFP-3D software written in the IgorPro (WaveMetrics Inc., Lake Oswego, OR) environment. Noncontact mode aluminum-coated silicon nitride cantilevers were purchased from NanoWorld (force constant = 42 N m^{-1}, resonance frequency = 320 kHz). All images were taken in air under ambient conditions.

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[1] S. D. Bergman, F. Wudl, *J. Mater. Chem.* **2008**, *18*, 41.
[2] R. P. Wool, *Soft Matter* **2008**, *4*, 400.
[3] D. Y. Wu, S. Meure, D. Solomon, *Prog. Polym. Sci.* **2008**, *33*, 479.
[4] M. W. Urban, *Prog. Polym. Sci.* **2009**, *34*, 679.
[5] S. R. White, N. R. Sottos, P. H. Geubelle, J. S. Moore, M. R. Kessler, S. R. Sriram, E. N. Brown, S. Viswanathan, *Nature* **2001**, *409*, 794.
[6] X. X. Chen, M. A. Dam, K. Ono, A. Mal, H. B. Shen, S. R. Nutt, K. Sheran, F. Wudl, *Science* **2002**, *295*, 1698.
[7] S. H. Cho, S. R. White, P. V. Braun, *Adv. Mater.* **2009**, *21*, 645.
[8] P. Cordier, F. Tournilhac, C. Soulie-Ziakovic, L. Leibler, *Nature* **2008**, *451*, 977.
[9] M. Yamaguchi, S. Ono, M. Terano, *Mater. Lett.* **2007**, *61*, 1396.
[10] K. Jud, H. H. Kausch, J. G. Williams, *J. Mater. Sci.* **1981**, *16*, 204.
[11] C. B. Lin, S. B. Lee, K. S. Liu, *Polym. Eng. Sci.* **1990**, *30*, 1399.
[12] M. Kawagoe, M. Nakanishi, J. Qiu, M. Morita, *Polymer* **1997**, *38*, 5969.
[13] D. G. Shchukin, H. Mohwald, *Small* **2007**, *3*, 926.
[14] D. V. Andreeva, D. Fix, H. Mohwald, D. G. Shchukin, *Adv. Mater.* **2008**, *20*, 2789.
[15] S. Gupta, Q. L. Zhang, T. Emrick, A. C. Balazs, T. P. Russell, *Nat. Mater.* **2006**, *5*, 229.
[16] S. H. Gehrke, *Adv. Polym. Sci.* **1993**, *110*, 81.
[17] J. C. Wheeler, J. A. Woods, M. J. Cox, R. W. Cantrell, F. H. Watkins, R. F. Edlich, *J. Long-Term Eff. Med. Implants* **1996**, *6*, 207.
[18] N. A. Peppas, J. Z. Hilt, A. Khademhosseini, R. Langer, *Adv. Mater.* **2006**, *18*, 1345.
[19] G. Decher, *Science* **1997**, *277*, 1232.
[20] J. A. Jaber, J. B. Schlenoff, *Curr. Opin. Colloid Interface Sci.* **2006**, *11*, 324.

[21] K. Ariga, J. P. Hill, Q. M. Ji, *Phys. Chem. Chem. Phys.* **2007**, *9*, 2319.
[22] M. J. Serpe, C. D. Jones, L. A. Lyon, *Langmuir* **2003**, *19*, 8759.
[23] M. J. Serpe, L. A. Lyon, *Chem. Mater.* **2004**, *16*, 4373.
[24] C. D. Sorrell, L. A. Lyon, *J. Phys. Chem. A* **2007**, *111*, 4060.
[25] H. Huang, J. Y. Chung, A. J. Nolte, C. M. Stafford, *Chem. Mater.* **2007**, *19*, 6555.
[26] G. T. Hermanson, *Bioconjugate Techniques*, Academic Press, San Diego, **1996**.
[27] C. M. Nolan, C. D. Reyes, J. D. Debord, A. J. Garcia, L. A. Lyon, *Biomacromolecules* **2005**, *6*, 2032.
[28] N. Singh, A. W. Bridges, A. J. Garcia, L. A. Lyon, *Biomacromolecules* **2007**, *8*, 3271.
[29] A. W. Bridges, N. Singh, K. L. Burns, J. E. Babensee, L. A. Lyon, A. J. Garcia, *Biomaterials* **2008**, *29*, 4605.
[30] A. S. Iyer, L. A. Lyon, *Angew. Chem.* **2009**, *121*, 4632; *Angew. Chem. Int. Ed.* **2009**, *48*, 4562.
[31] Y. D. Yi, Y. C. Bae, *J. Appl. Polym. Sci.* **1998**, *67*, 2087.
[32] J. D. Debord, L. A. Lyon, *J. Phys. Chem. B* **2000**, *104*, 6327.
[33] C. M. Nolan, M. J. Serpe, L. A. Lyon, *Biomacromolecules* **2004**, *5*, 1940.
[34] M. J. Serpe, K. A. Yarmey, C. M. Nolan, L. A. Lyon, *Biomacromolecules* **2005**, *6*, 408.
[35] C. Sorrell, D. , L. A. Lyon, *J. Phys. Chem. B* **2007**, *111*, 4060.

