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Low Power, Biologically Benign NIR Light Triggers Polymer Disassembly

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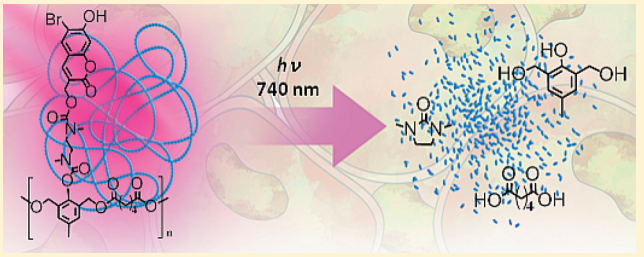
Supporting Information

ABSTRACT: Near infrared (NIR) irradiation can penetrate up to 10 cm deep into tissues and be remotely applied with high spatial and temporal precision. Despite its potential for various medical and biological applications, there is a dearth of biomaterials that are responsive at this wavelength region. Herein we report a polymeric material that is able to disassemble in response to biologically benign levels of NIR irradiation upon two-photon absorption. The design relies on the photolysis of the multiple pendant 4-bromo7-hydroxycoumarin protecting groups to trigger a cascade of cyclization and rearrangement reactions leading to the degradation of the polymer backbone. The new material undergoes a 50% M_w loss after 25 s of ultraviolet (UV) irradiation by single photon absorption and 21 min of NIR irradiation via two-photon absorption. Most importantly, even NIR irradiation at a biologically benign laser power is sufficient to cause significant polymer disassembly. Furthermore, this material is well tolerated by cells both before and after degradation. These results demonstrate for the first time a NIR sensitive material with potential to be used for *in vivo* applications.



INTRODUCTION

Smart polymeric materials are presently one of the main focuses in biomedical materials research. These types of materials respond to subtle environmental changes in a controlled, predictable way, which makes them useful tools for tissue engineering,[1−10] implants[1,11−14] and wound healing,[15] drug delivery[9,16−19] and biosensors.[20−25] Various internal and external triggers, such as pH,[26−29] specific enzymes,[30−36] temperature,[4,37−41] ultrasound,[42−44] magnetic field[17,45,46] and light[18,45,47−56] are being explored. Optical stimulus is especially attractive as it can be remotely applied for a short period of time with high spatial and temporal precision. A large number of light-degradable materials (micelles,[57,58] polymeric nanoparticles[59] and bulk hydrogels[60,61]) have been reported recently. However, most of the materials reported respond to NIR light by undergoing a hydrophobicity switch[62−65] and the photodegradation products are high molecular weight linear or cross-linked polymer fragments that may be difficult to clear from the body. Additionally, most of the reported light-degradable materials respond efficiently to UV irradiation. Near infrared (NIR) light can penetrate up to 10 cm deep into tissue[66] with less damage and absorption or scattering and is more desirable for *in vivo* applications.[67−69] Despite these advantages, only a handful of organic materials reported to date can respond to high power NIR light due to the inefficient two photon absorption process. None are able to respond to low power NIR light which is important to biological applications because it causes less photodamage to tissue and cells.[70] For *in vivo* applications, it would be more advantageous to have a material that degrades into small fragments upon NIR light exposure, which can then be easily excreted, with less long-term risks. Therefore, we designed a linear synthetic polymer with multiple pendant light-sensitive triggering groups in such a way that once these groups are cleaved, a cascade of cyclization and rearrangement reactions is triggered, leading to backbone degradation.[48] The first proof-of-concept polymer utilized a commercially available and well-studied *o*-nitrobenzyl (ONB) triggering group, which was attached to the polymer backbone via a diamine linker. ONB groups are widely used in synthetic chemistry as protecting groups for alcohols and amines, which can be readily removed with UV light. They were also shown to photolyze upon NIR irradiation via two-photon excitation, although their two-photon uncaging cross sections (a quantitative measure of the efficiency of a molecule to simultaneously absorb two photons of light and convert that energy into a chemical reaction) are very low.[71] Consequently, several hours of continuous NIR irradiation at high laser power were required to trigger the polymer degradation. Another drawback of the ONB triggering group is potential toxicity of nitrosobenzaldehyde, the product of photocleavage of ONB groups. Clearly, the reported polymer required further modification in order to become a practically useful material. The material we are reporting here utilizes another well-known photocleavable group, 4-bromo7-hydroxycoumarin (Bhc), which

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has a much higher two-photon uncaging cross-section,[72−74] and produces no toxic byproducts upon cleavage. Introduction of the new triggering group drastically increases the sensitivity of the material to NIR light, reducing the exposure time required to produce appreciable polymer degradation to a few minutes. Moreover, we show that laser power as low as 200 mW is sufficient to trigger polymer fragmentation. To our knowledge, this is the only polymeric material specifically designed to disassemble into small fragments in response to biologically benign levels of NIR irradiation.

EXPERIMENTAL SECTION

General Methods and Instrumentation. 2,6-Bis(hydroxymethyl)-*p*-cresol and 4-bromoresorcinol were purchased from Acros Organics and used as received. 4,5-Dimethoxy-2-nitrobenzyl alcohol and *N*,*N*-dimethylethylenediamine was purchased from Sigma-Aldrich and used as received. Amberlyst 15 (dry resin) was purchased from Supelco. Adipoyl chloride was purchased from Aldrich and purified by vacuum distillation. All reactions requiring anhydrous conditions were performed under a nitrogen atmosphere. Flash chromatography was performed using a CombiFlash Companion system. ^{1}H NMR spectra were acquired using a Joel 500 MHz spectrometer or a Varian 400 MHz spectrometer. ^{13}C NMR spectra were acquired using a Varian spectrometer operated at 100 MHz. UV spectra were collected using a Shimadzu UV-3600 UV−vis-NIR Spectrophotometer. Degradation of the monomers containing Bhc and ONB triggering groups (designated **BhcM** and **ONBM**) was monitored by an Agilent 1200 HPLC equipped with PDA and MSD detectors and a C18 column with 0.1% formic acid/H_2O and 0.1% formic acid/acetonitrile as eluents at a flow rate of 0.3 mL/min. The molecular weights of the polymers, **BhcP** and **ONBP** (where P denotes polymer), were measured relative to polystyrene standards using a Waters e2196 Series HPLC system equipped with RI and PDA detectors and a Waters Styragel HR 2 size-exclusion column with 0.1% LiBr/DMF as eluent and flow rate of 1 mL/min at 37°C. For irradiation with UV light, a Luzchem LZC-ORG photoreactor equipped with 8 UV-A lamps (350 nm maximum intensity, 8 W) was used. A Ti:sapphire laser (Mai Tai HP, Spectra Physics) with ∼100 fs pulse widths and 80 MHz repetition rate generated light for NIR irradiation. For monomer and polymer degradation by NIR, 2.5 W (4 kW/cm^2) of 750 nm (for **ONBM** and **ONBP**) and 740 nm (for **BhcM** and **BhcP**) light was focused into the solution using a EFL 33.0 mm lens. Low power irradiation experiments used 200 mW (0.32 kW/cm^2) of 740 nm light (2.5 nJ/pulse for the laser repetition rate) attenuated with a wave plate/polarizer combination.

Compounds **2** and **3** were synthesized according to a previously published procedure.[75] Compound **9** was synthesized according to a previously published procedure.[74] Compounds **4** and **10** were synthesized according to a previously published procedure.[73] Their ^{1}H NMR spectra were in agreement with the published data and the experimental details are provided in the Supporting Information. The synthesis of **ONBM** and **ONBP** is described in a previous publication.[48]

Compound 5. Compound **3** (0.5 g, 0.89 mmol) in 10 mL DCM was added dropwise over 30 min to a solution of *N*,*N*-dimethylethylenediamine in 15 mL of DCM and 5 mL of DMF at 0°C. After 30 min the solvents and excess of *N*,*N*-dimethylethylenediamine were removed on rotovap and reaction mixture was dissolved in 4 mL of dry DMF and Et_3N (0.8 mL) and compound 4 were added. The reaction was stirred at room temperature for 1 h, after that the solvents were removed on rotovap and the residue was purified by flash-chromatography on cyano-modified silica gel with hexanes/ethyl acetate (100%/0% to 0%/100%) as eluent. Yield: 0.39 g (51%).

^{1}H NMR (500 MHz, $CDCl_3$): 7.70 (s, 1H), 7.17−7.12 (m, 3H), 6. 31 (s, 1H), 5.31 (s, 2H), 5.28−5.25 (m, 2H), 4.63−4.58 (m, 4H), 3.62−3.53 (m, 4H), 3.51 (s, 3H), 3.61−3.00 (m, 6H), 2.32 (s, 3H), 0.9 (s, 18H), 0.06 (s, 12H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 160.38, 156.33, 155.17, 154.93, 154.26, 149.20, 143.20, 135.54, 133.43, 127.68, 115.60, 112.57, 106.66, 104.14, 95.25, 64.26, 62.56, 62.18, 60.57, 60.39, 56.82, 48.33, 47.29, 35.60, 26.04, 18.51, −5.13 ppm.

HRMS: measured mass, 873.2780; theoretical mass, 873.2784; composition, $C_{39}H_{59}N_2O_{10}BrSi_2Na$.

Compound 6. Compound **5** (0.11 g,) was dissolved 15 mL of MeOH and 2 mL of DCM, Amberlyst 15 was added and reaction was stirred at room temperature for 2 h. The catalyst was filtered off, solvents were removed on rotovap and the residue was purified by flash-chromatography on silica gel with hexanes/ethyl acetate (70%/30%-0%/100%). Yield: 0.059 g (74%).

^{1}H NMR (400 MHz, $CDCl_3$): 7.73−7.67 (m, 1H), 7.18−7.04 (m, 3H), 6.36−6.26 (m, 1H), 5.30−5.24 (m, 4H), 4.51−4.43 (m, 4H), 3.69−3.56 (m, 4H), 3.51 (s, 3H), 3.20−3.03 (m, 6H), 2.31 (s, 3H) ppm.

^{13}C (100 MHz, CDCl3): 160.84, 156.69, 154.14, 149.68, 145.04, 136.27, 133.22, 130.16, 127.69, 110.75, 109.57, 106.91, 104.05, 95.69, 95.21, 64.20, 62.38, 60.56, 56.81, 55.50, 46.94, 35.18, 20.94 ppm.

HRMS: theoretical mass, 645.1054; measured mass, 645.1050; composition, $C_{27}H_{31}BrN_2O_{10}Na$.

BhcM. Compound **6** (0.12 g, 0.137 mmol) was dissolved in 1 mL of DCM, and 1 mL of TFA was added. The reaction mixture was stirred at room temperature and monitored by TLC (ethyl acetate/hexane =7/3). After the reaction was completed, solvents were removed on high vacuum, and crude product was purified by flash-chromatography on silica gel with hexanes/ethyl acetate (70%/30% to 0%/100%). Yield: 0.05 g (61%).

^{1}H NMR (400 MHz, DMSO): 7.68−7.64 (m, 1H), 7.38−7.27 (m, 2H), 7.00−6.97 (m, 1H), 6.36−6.27 (m, 1H), 5.32−5.27 (m, 6H), 3.64−3.53 (m, 4H), 3.19−3.05 (m, 6H), 2.38−2.35 (m, 3H) ppm.

^{13}C (100 MHz, DMSO): 159.71, 157.47, 154.97, 153.81, 150.75, 142.80, 134.47, 134.08, 128.50, 126.18, 110.51, 108.35, 106.23, 103.23, 62.03, 57.70, 46.60, 46.05, 35.06, 34.37, 33.81, 20.89 ppm.

HRMS: theoretical mass, 601.0787; measured mass, 601.0792; composition, $C_{25}H_{27}BrN_2O_9Na$.

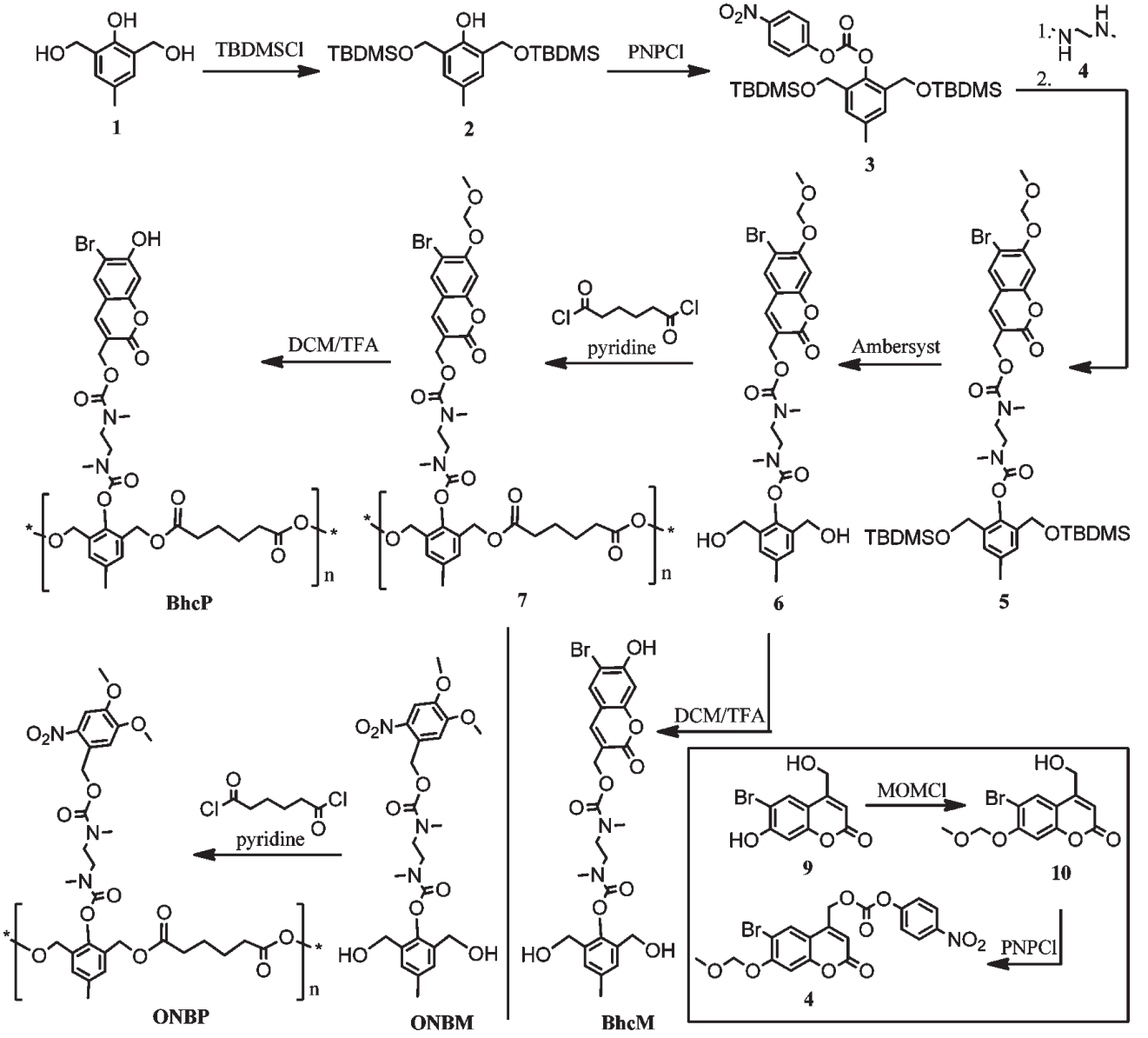
BhcP. Monomer **6** (0.2 g, 0.32 mmol) and adipoyl chloride (0.046 mL, 0.32 mmol) were dissolved in 2 mL of DCM under nitrogen, and pyridine (0.156 mL, 1.92 mmol) was added to the reaction mixture dropwise over 10 min. The polymerization was allowed to proceed overnight at room temperature. The reaction mixture was concentrated on a rotovap to 0.2 mL and precipitated into 5 mL of cold EtOH, yielding waxy polymer product **7**. Compound **7** was dissolved in 0.5 mL of DCM, and 0.5 mL of TFA was added. The solution was stirred for 30 min at room temperature. The solvents were removed on rotovap. The oligomers were removed by repeated precipitation of the polymer solution in DCM into cold MeOH. Yield: 63% (white solid).

^{1}H NMR (500 MHz, $CDCl_3$): 7.62 (s, 1H), 7.23−7.13 (m, 2H), 6.67 (s, 1H), 6.31 (s, 1H), 5.29 (s, 2H), 5.00 (s, 4H), 3.65−3.46 (m, 4H), 3.17−3.04 (m, 6H), 2.29 (s, 6H), 1.64 (s, 3H) ppm.

^{13}C (100 MHz, DMSO): 159.60, 157.51, 153.75, 150.48, 145.01, 129.16, 128.30, 110.47, 108.41, 106.21, 103.16, 61.94, 60.74, 60.57, 35.00, 33.40, 33.29, 32.94, 24.04, 23.93, 23.78, 23.71, 20.61, 20.37 ppm.

UV and NIR Degradation of ONBM and BhcM. Solutions of **ONBM** and **BhcM** in PBS pH 7.4 (1 mg/mL), with 4-hydroxy-benzoic acid-*n*-hexyl ester as an internal standard, were placed in quartz semi-micro spectrophotometer cells (10 mm path length) and irradiated with UV light for certain periods of time. For NIR irradiation experiments, the solutions of **ONBM** and **BhcM** were placed in 50 μL quartz cells with 3 mm path length and irradiated at 740 and 750 nm, respectively. The irradiated solutions were injected into HPLC and chromatograms at 280 nm were recorded. The fraction of the remaining caged compounds was calculated by integrating the peaks of **ONBM** and **BhcM** relative to the peak of the internal standard.

Scheme 1. Synthetic Route to BhcM and BhcP and the Structures of ONBM and ONBP



UV and NIR Degradation of ONBP and BhcP. For UV degradation of the polymers, solutions of **ONBP** and **BhcP** (0.1 mg/mL) in a mixture of acetonitrile and PBS 7.6 (9:1 and 7:3, respectively) were placed into quartz semimicro spectrophotometer cells (10 mm path length) and irradiated with UV light inside a photoreactor for certain periods of time. The irradiated solutions were incubated at 37°C for 96 h. The solvents were removed on vacuum. The organic residue was dissolved in DMF and injected into GPC. In the NIR irradiation experiments, for each data point three separate solutions containing **ONBP** or **BhcP** were irradiated for the given time and combined for incubation at 37°C followed by solvent removal and dissolution in DMF to achieve acceptable signal-to-noise ratio in GPC.

RESULTS AND DISCUSSION

Synthesis of BhcM and BhcP. In order to install the 7-hydroxy-4-bromocoumarin triggering group we modified the previously published scheme for **ONBP**[48] resulting in a synthetic route to **BhcP** shown in Scheme 1. We started with commercially available 2,6-bis(hydroxymethyl)-*p*-cresol, **1**, and selectively protected the benzylic alcohols with TBDMSCl in the presence of imidazole to obtain compound **2** in 87.5% yield. Activated carbonate **3** was obtained in 85% yield by reacting compound **2** with PNPCl in the presence of DMAP and Et_3N in DCM. *N*,*N*-Dimethylethylene diamine was reacted with compound **3** at a stoichiometric ratio of 3 to 1 to achieve conversion of only one amino group of the diamine into a carbamate. Excess *N*,*N*-dimethylethylene diamine was removed and the coumarin derivative **4** was added into the reaction mixture to obtain compound **5** in 51% yield. The TBDMS protecting groups were removed with Amberlyst-15 (74% yield). Monomer **6** was co-polymerized with adipoyl chloride in DCM in the presence of pyridine to afford polymer **7**. Finally, the MOM protective groups were removed in DCM/TFA solution to afford the final polymer, **BhcP**. Low molecular weight oligomers were removed by precipitating the polymer into ice-cold MeOH. The combined

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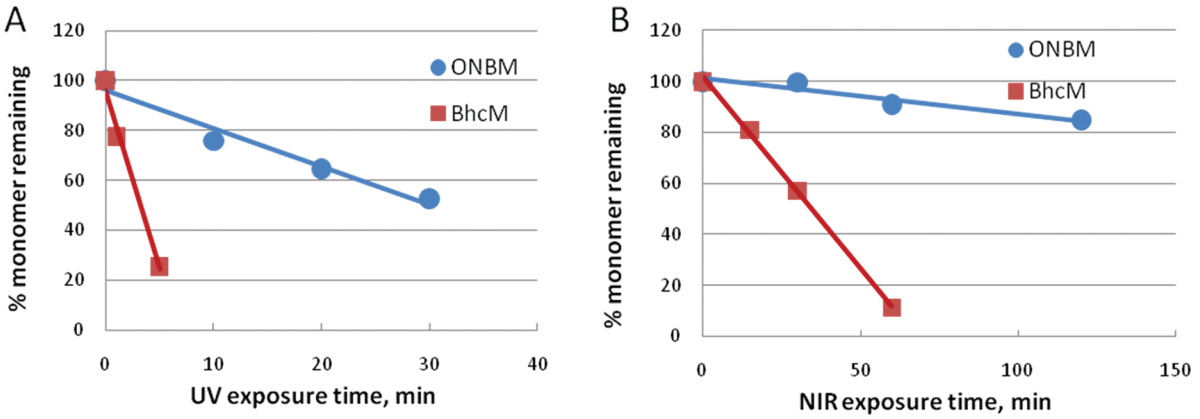
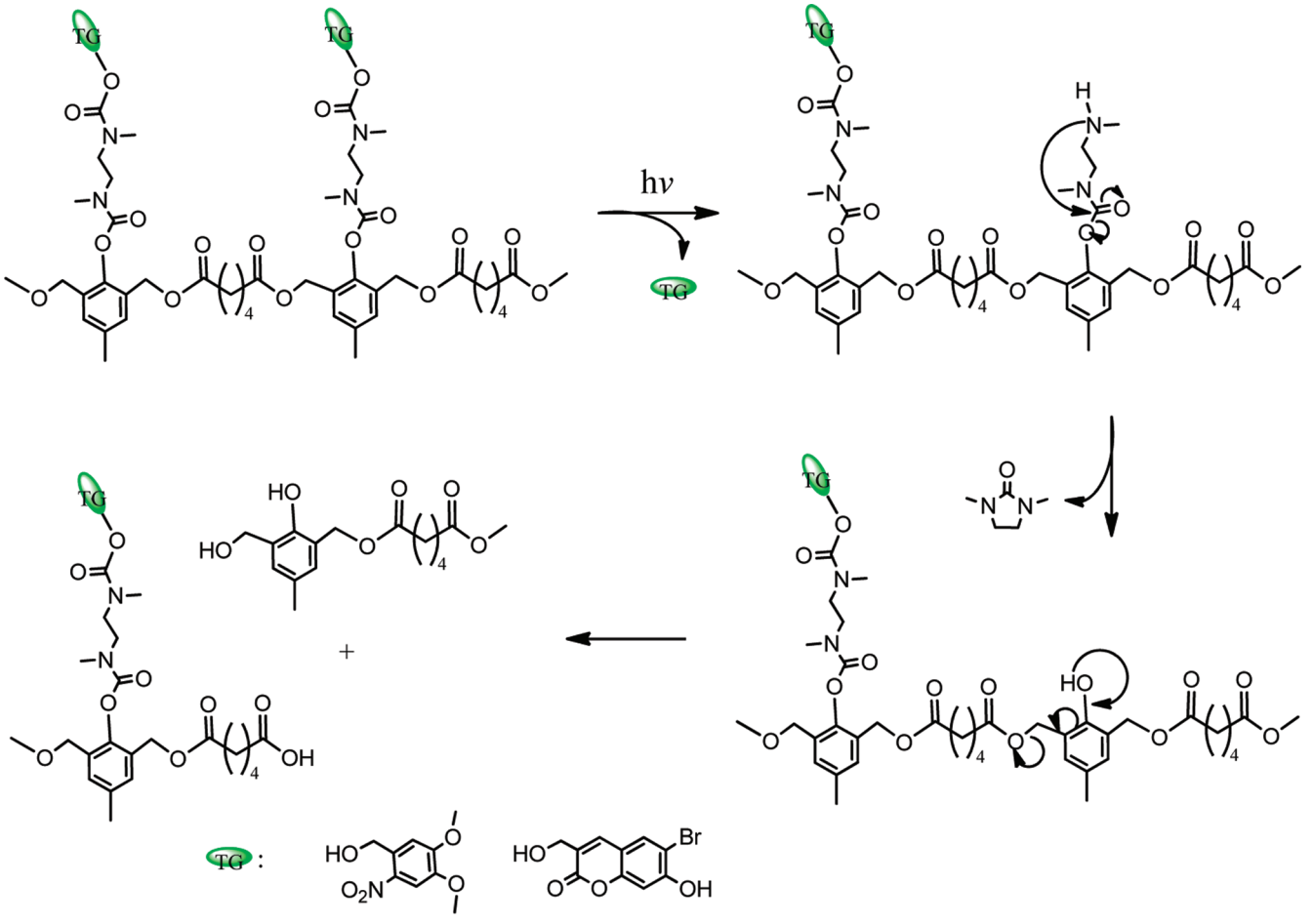


Figure 1. Disappearance of **ONBM** and **BhcM** upon UV irradiation (A) and NIR (B) irradiation.

Scheme 2. Degradation Mechanism of a Light-Sensitive Polymer Incorporating a Quinone−Methide Moiety[a]



[a] TG = triggering group.

yield of **BhcP** after the polymerization and deprotection steps was 63%. The molecular weight (M_w) of **BhcP** was determined by GPC to be 31 500 Da (PDI = 1.09) relative to PS standards.

BhcM was obtained in 61% from compound **6** by removing the MOM protective group in a mixture of TFA and DCM.

Degradation of ONBM and BhcM. To compare the rates of cleavage of the ONB and Bhc triggering groups, solutions of **ONBM** and **BhcM** were first exposed to 350 nm light for certain time periods and injected into the HPLC. The formation of nitrosobenzaldehyde and 4-bromo-7-hydroxycoumarin confirmed the photolysis of **ONBM** and **BhcM**. Figure 1A shows

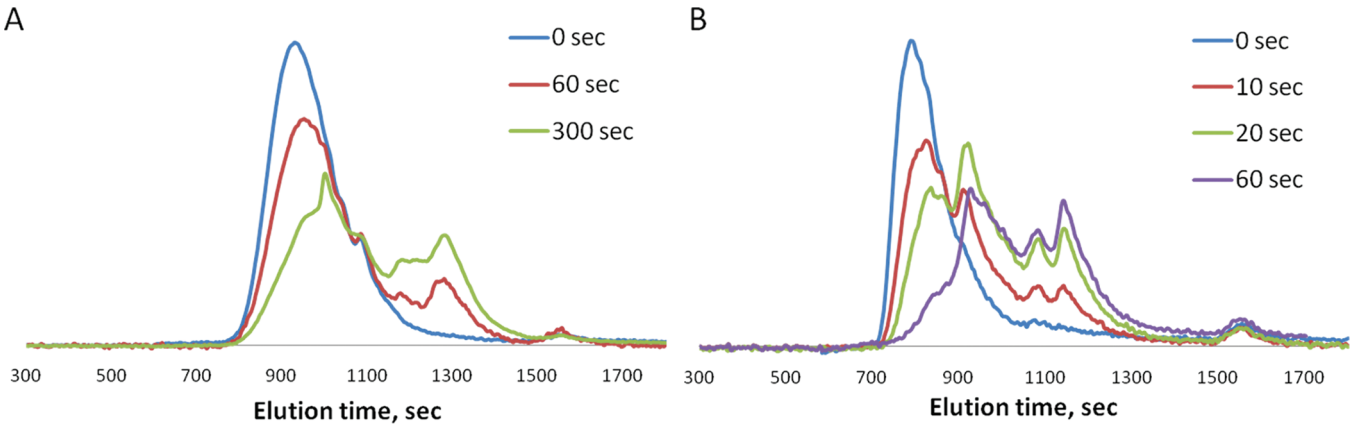


Figure 2. GPC chromatograms of **ONBP** (A) and **BhcP** (B) after UV exposure for 0, 10, 20, 60, or 300 s and incubation at 37°C for 96 h.

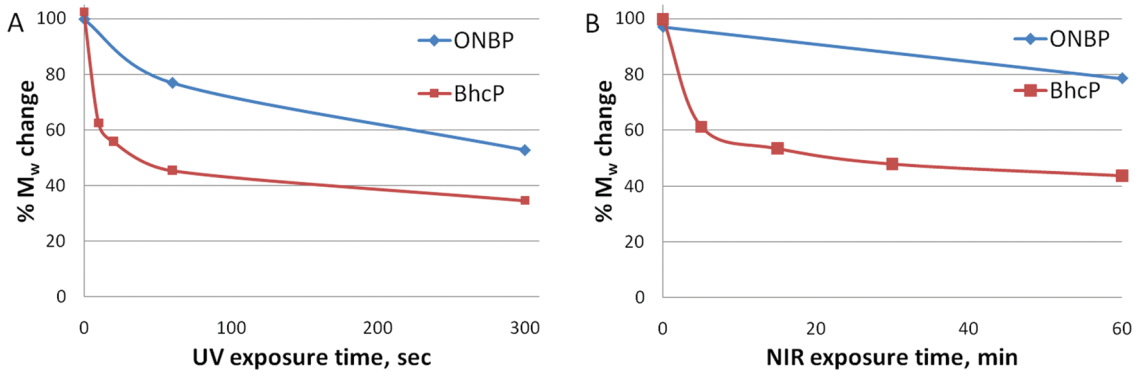


Figure 3. Decrease of the M_w of **ONBP** and **BhcP** as a function of exposure time to UV light (A) and NIR light (B).

the percentage of remaining monomer, calculated relative to an internal standard, as a function of UV exposure time for **ONBM** and **BhcM**. The rate of photolysis of **BhcM** was 10 times higher compared to **ONBM**, consistent with the previous reports of one-photon uncaging quantum yields of other alcohols and amines.[72−74] Comparing the red and blue traces in Figure 1A, 50% of the Bhc groups were cleaved after 3.2 min of irradiation, while 30.18 min irradiation was required to cleave 50% of ONB groups. The same 10-fold difference in the rates of triggering group cleavage was observed upon NIR irradiation of the monomers. Figure 1B shows 50% of Bhc groups were cleaved after 34 min versus 370 min for ONB groups. The Bhc protecting group shows a higher two photon absorption due to the increased π-conjugation length which leads to a higher dipole moment induced by the electric field of a light wave.[76] Additionally, the introduction of halogen atoms enhances intersystem crossing and therefore improves the photolysis quantum yield.[74] Consequently, a large difference in the two-photon uncaging cross sections of the two triggering groups could be expected. However, it is difficult to predict by how much the cleavage rate will change when switching from one caging group to the other, since the uncaging efficiency is affected by many factors, such as the structure of the leaving group, the solvent and the wavelength and the power of the laser used in the experiment. The reported two-photon uncaging of acetic acid by Bhc and ONB-protected esters at 740 nm was 1.99 GM and 0.03 GM, respectively (66-fold difference) and 0.42 GM and 0.01 GM at 800 nm (42-fold difference).[74] Uncaging of L-glutamic acid by Bhc ester was only 0.95 GM.[74] It should also be mentioned that in our experiments the **ONBM** and **BhcM** were irradiated with 750 and 740 nm of light, respectively, to account for the difference in the two-photon absorption maxima of the two groups. However, given the very short pulse widths of our laser, this difference in wavelength is likely not a large factor in the differences between our degradation rates and previously reported uncaging cross sections.

Degradation of ONBP and BhcP. Scheme 2 shows the mechanism of degradation of light-sensitive polymers containing a quinone-methide self-immolative moiety.[75,77,78] The degradation starts when a triggering group is cleaved upon irradiation with either UV or NIR light, releasing an amino group. *N*,*N*-Dimethylethylene diamine linker cyclizes, unmasking an unstable phenol. The quinone-methide rearrangement of the phenol results in the cleavage of the polymer backbone.

Degradation of the polymers containing ONB and Bhc triggering groups was studied in acetonitrile: PBS pH 7.6 (9:1 and 7:3, respectively). These combinations of solvents were found suitable to fully dissolve the polymers. The solutions were irradiated with UV light for 0, 10, 20, 60, and 300 s, incubated at 37°C for 96 h and analyzed by GPC. As we have shown previously for ONBP,[48] the polymer degradation is complete in 4 days in neutral pH. The chromatograms of **ONBP** and **BhcP** after UV exposure are shown in Figure 2. For both polymers, the GPC traces shift to longer elution times after irradiation and shorter fragments are formed. However, much shorter irradiation times are required to produce a significant reduction in the molecular weight of **BhcP** compared to **ONBP**. Plotting the

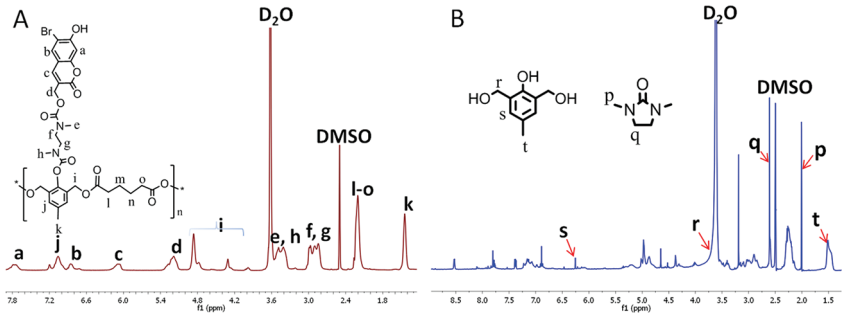


Figure 4. ^{1}H NMR spectra of **BhcP** in DMSO-d_6: D_2O (6:1) before (A) and after (B) UV exposure.

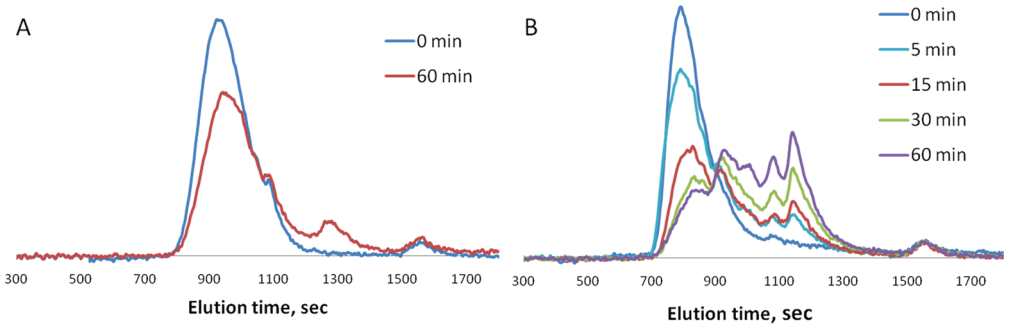


Figure 5. GPC chromatograms of **ONBP** (A) and **BhcP** (B) after exposure to NIR for 0, 5, 15, 30, or 60 min and incubation at 37°C for 96 h.

percent change in the molecular weight of the polymers as a function of irradiation time (Figure 3A) reveals that **BhcP** degrades 10 times faster than **ONBP**, as could be expected from the monomers' degradation rates. Thus, M_w of **BhcP** decreases by 50% after 25 s of UV irradiation compared to 300 s in the case of **ONBP**. In the control experiment, the solutions of **ONBP** and **BhcP** not exposed to UV or NIR irradiation were incubated at 37°C for 96 h. The molecular weights of the polymers remained unchanged, demonstrating that backbone fragmentation is controlled exclusively by the removal of the triggering groups and no dark hydrolysis takes place during this time.

In order to confirm the degradation mechanism of **BhcP**, the polymer was exposed to UV irradiation in DMSO$_{d6}$: D_2O (6:1) and incubated for 72 h at 37°C. The expected degradation products, 2,6-bis(hydroxymethyl)-*p*-cresol and 1,3-dimethyl-2-imidazolidinone, were identified in the ^{1}H NMR spectrum of the partially degraded **BhcP** (Figure 4). The methyl group of cresol (t) appears at 1.52 ppm, shifted downfield compared to the methyl groups of cresol incorporated into the polymer (k, 1.44 ppm). The aromatic protons (s) appear as a sharp singlet at 6.26 ppm. The signal from the benzylic protons (r) is obscured by the signal from D_2O. The signals of 1,3-dimethyl-2-imidazolidinone appear very distinctly at 2.01 and 2.61 ppm. The peak assignments were confirmed by taking the spectra of the pure 2,6-bis-(hydroxymethyl)-*p*-cresol and 1,3-dimethyl-2-imidazolidinone in DMSO$_{d6}$: D_2O (6:1).

Having confirmed that **BhcP** degrades in the way it was designed to, we moved to the degradation experiments using NIR light. The polymer was irradiated for 5, 15, 30, and 60 min and incubated for 96 h at 37°C. The GPC chromatograms after 96 h of incubation are shown in Figure 5. Similar to UV irradiation, a significant drop in the intensity of the high molecular weight peak

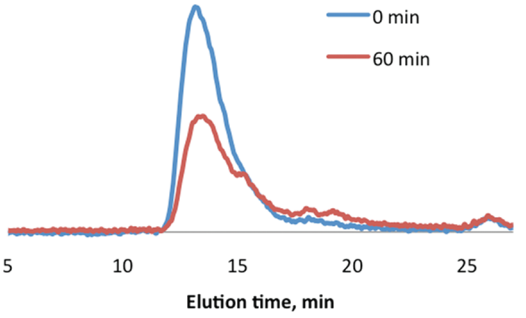


Figure 6. GPC chromatograms of **BhcP** after exposure to low energy NIR irradiation for 60 min and incubation at 37°C for 96 h.

and appearance of the low molecular weight fragments were observed. In comparison with **ONBP**, much shorter irradiation times were required to produce significant fragmentation of **BhcP**. Figure 2B shows 50% molecular weight loss was achieved after 21 min of NIR irradiation of **BhcP**, while for **ONBP** 1 h of continuous irradiation only resulted in 20% weight loss. Attempted irradiation of **ONBP** for more than 60 min to achieve 50% molecular weight loss resulted in evaporation of acetonitrile, which caused precipitation of **ONBP** from solution. Nevertheless, comparison of the degradation profiles of **ONBP** and **BhcP** after 60 min of irradiation confirms significantly improved NIR sensitivity of the polymer containing the Bhc triggering group.

Even though NIR irradiation is considered more benign than UV wavelengths, there is a certain energy threshold above which photodamage will occur. Watanabe et al demonstrated that laser energies between 2 nJ/pulse and 4 nJ/pulse did not produce any damage to living cells.[70] Therefore, we attempted NIR light

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degradation of **BhcP** within this range (200 mW, corresponding to 2.5 nJ/pulse) to further demonstrate the practicality of using this material for *in vivo* applications. Exposure of the **BhcP** solution to low power NIR irradiation for 60 min resulted in the 29% drop in the molecular weight (Figure 6). This further illustrates the improvement achieved by using Bhc instead of ONB as a triggering group considering that after an hour of irradiation of **ONBP** at full laser power there was only a 20% decrease in molecular weight of the polymer. Furthermore, this experiment confirms that the polymer degradation is caused by the two-photon absorption process and not simply by possible heat generated by the laser, since at 200 mW heat generation is less likely.[79]

We investigated the cytotoxicity of **BhcP** by incubating various concentrations of it with cells and monitoring the cellular metabolic activity via a MTT assay. Measurements taken before and after irradiation show that the polymer and its degradation products are well tolerated by cells (Figure S1, Supporting Information).

It has been reported that absorption properties and photolysis quantum yields of coumarin triggering groups are strongly affected by the polarity and hydrophobicity of the medium. For example, the quantum yield of a Bhc-protected galactose derivative in 10 mM KMops, pH 7.2 containing 25% acetonitrile was two times lower than in 10 mM KMops, pH 7.2 containing 0.1% DMSO.[73] Therefore, we did not expect that **BhcP** would maintain its high light sensitivity in bulk, since in this case the polymer backbone would create a local hydrophobic environment. Therefore, we envision further applications of this material in hydrogel systems where unrestricted access of water will allow for high photolysis quantum yields.

CONCLUSIONS

In conclusion, a new polymeric material capable of triggered disassembly upon irradiation with biologically benign levels of NIR light was developed. This material disassembles via photocleavage of Bhc groups with unprecedented sensitivity to NIR light. A 29% decrease in M_w of BhcP was observed after irradiation with 200 mW NIR light. To the best of our knowledge, this is the first example of a polymeric material capable of disassembly into small molecules in response to harmless levels of irradiation. Notably, cell toxicity assays reveal excellent tolerance of cells to this polymer before and after irradiation and subsequent disassembly. This system is an excellent first step, however, further studies are warranted to improve the sensitivity of polymeric materials to NIR. We are currently pursuing several synthetic and engineering strategies to this end.

ASSOCIATED CONTENT

Supporting Information. Details for the synthesis of compounds **2**, **3**, **4**, **9** and **10** and cytotoxicity experiments. This material is available free of charge via the Internet at http://pubs.acs.org/.

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REFERENCES

(1) Barrere, F.; Mahmood, T. A.; de Groot, K.; van Blitterswijk, C. A. *Mater. Sci. Eng. R-Rep.* **2008**, *59*, 38.
(2) Blan, N. R.; Birla, R. K. *J. Biomed. Mater. Res., Part A* **2008**, *86A*, 195.
(3) Cao, Y.; Li, H. B. *Nat. Nanotechnol.* **2008**, *3*, 512.
(4) Da Silva, R. M. P.; Mano, J. F.; Reis, R. L. *Trends Biotechnol.* **2007**, *25*, 577.
(5) Ehrbar, M.; Rizzi, S. C.; Hlushchuk, R.; Djonov, V.; Zisch, A. H.; Hubbell, J. A.; Weber, F. E.; Lutolf, M. P. *Biomaterials* **2007**, *28*, 3856.
(6) Galler, K. M.; D'Souza, R. N. *Regener, Med.* **2011**, *6*, 111.
(7) Giselbrecht, S.; Gietzelt, T.; Gottwald, E.; Trautmann, C.; Truckenmuller, R.; Weibezahn, K. F.; Welle, A. *Biomed. Microdevices* **2006**, *8*, 191.
(8) Mieszawska, A. J.; Kaplan, D. L. *BMC Biol.* **2010**, *8*, No. in press.
(9) Moroni, L.; De Wijn, J. R.; Van Blitterswijk, C. A. *J. Biomater. Sci., Polym. Ed.* **2008**, *19*, 543.
(10) Prabhakaran, M. P.; Venugopal, J.; Kai, D.; Ramakrishna, S. *Mater. Sci. Eng. C-Mate. Biol. Appl.* **2011**, *31*, 503.
(11) Evans, A. T.; Chiravuri, S.; Gianchandani, Y. B. *Biomed. Microdevices* **2010**, *12*, 179.
(12) Giordano, C.; Chiesa, R.; Sandrini, E.; Cigada, A.; Giavaresi, G.; Fini, M.; Giardino, R. *J. Mater. Sci., Mater. Med.* **2005**, *16*, 1221.
(13) Jayant, R. D.; McShane, M. J.; Srivastava, R. *Int. J. Pharm.* **2011**, *403*, 268.
(14) Zhang, Q. W.; Mochalin, V. N.; Neitzel, I.; Knoke, I. Y.; Han, J. J.; Klug, C. A.; Zhou, J. G.; Lelkes, P. I.; Gogotsi, Y. *Biomaterials* **2011**, *32*, 87.
(15) Sabolinski, M. L.; Alvarez, O.; Auletta, M.; Mulder, G.; Parenteau, N. L. *Biomaterials* **1996**, *17*, 311.
(16) Gong, C. B.; Wong, K. L.; Lam, M. H. W. *Chem. Mater.* **2008**, *20*, 1353.
(17) Peng, S. L.; Zhang, M. Y.; Niu, X. Z.; Wen, W. J.; Sheng, P.; Liu, Z. Y.; Shi, J. *Appl. Phys. Lett.* 2008, *92*.
(18) Gong, C. B.; Lam, M. H. W.; Yu, H. X. *Adv. Funct. Mater.* **2006**, *16*, 1759.
(19) Hoffman, A. S.; Stayton, P. S.; Press, O.; Murthy, N.; Lackey, C. A.; Cheung, C.; Black, F.; Campbell, J.; Fausto, N.; Kyriakides, T. R.; Bornstein, P. *Polym. Adv. Technol.* **2002**, *13*, 992.
(20) Duceppe, N.; Tabrizian, M. *Expert Opin. Drug Delivery* **2010**, *7*, 1191.
(21) Gant, R. M.; Hou, Y. P.; Grunlan, M. A.; Cote, G. L. *J. Biomed. Mater. Res., Part A* **2009**, *90A*, 695.
(22) Guan, B.; Magenau, A.; Kilian, K. A.; Ciampi, S.; Gaus, K.; Reece, P. J.; Gooding, J. J. *Faraday Discuss.* **2011**, *149*, 301.
(23) Guo, Y.; Xia, F.; Xu, L.; Li, J.; Yang, W. S.; Jiang, L. *Langmuir* **2010**, *26*, 1024.
(24) Lin, G.; Chang, S.; Hao, H.; Tathireddy, P.; Orthner, M.; Magda, J.; Solzbacher, F. *Sens. Actuators, B: Chem.* **2010**, *144*, 332.
(25) Song, J.; Cheng, Q.; Zhu, S. M.; Stevens, R. C. *Biomed. Microdevices* **2002**, *4*, 213.
(26) Murthy, N.; Xu, M. C.; Schuck, S.; Kunisawa, J.; Shastri, N.; Frechet, J. M. J. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 4995.
(27) Liu, X. M.; Wang, L. S. *Biomaterials* **2004**, *25*, 1929.
(28) Sankaranarayanan, J.; Mahmoud, E. A.; Kim, G.; Morachis, J. M.; Almutairi, A. *ACS Nano* **2010**, *4*, 5930.
(29) Xiang, Y. Q.; Chen, D. J. *Eur. Polym. J.* **2007**, *43*, 4178.
(30) Veronese, F. M.; Schiavon, O.; Pasut, G.; Mendichi, R.; Andersson, L.; Tsirk, A.; Ford, J.; Wu, G. F.; Kneller, S.; Davies, J.; Duncan, R. *Bioconjugate Chem.* **2005**, *16*, 775.
(31) Saez, J. A.; Escuder, B.; Miravet, J. F. *Tetrahedron* **2010**, *66*, 2614.
(32) Vemula, P. K.; Cruikshank, G. A.; Karp, J. M.; John, G. *Biomaterials* **2009**, *30*, 383.
(33) Khelfallah, N. S.; Decher, G.; Mesini, P. J. *Biointerphases* **2007**, *2*, 131.
(34) Romberg, B.; Flesch, F. M.; Hennink, W. E.; Storm, G. *Int. J. Pharm.* **2008**, *355*, 108.

(35) Khelfallah, N. S.; Decher, G.; Mesini, P. J. *Macromol. Rapid Commun.* **2006**, *27*, 1004.
(36) Igari, Y.; Kibat, P. G.; Langer, R. *J. Controlled Release* **1990**, *14*, 263.
(37) Tian, B. S.; Yang, C. *J. Nanosci. Nanotechnol.* **2011**, *11*, 1871.
(38) Eissa, A. M.; Khosravi, E. *Eur. Polym. J.* **2011**, *47*, 61.
(39) Lowik, D. W. P. M.; Leunissen, E. H. P.; van den Heuvel, M.; Hansen, M. B.; van Hest, J. C. M. *Chem. Soc. Rev.* **2010**, *39*, 3394.
(40) Gao, J. A.; Liu, Y. L.; Xu, H. P.; Wang, Z. Q.; Zhang, X. *Langmuir* **2010**, *26*, 9673.
(41) Collett, J.; Crawford, A.; Hatton, P. V.; Geoghegan, M.; Rimmer, S. *J. R. Soc. Interface* **2007**, *4*, 117.
(42) Yu, X. D.; Liu, Q. A.; Wu, J. C.; Zhang, M. M.; Cao, X. H.; Zhang, S.; Wang, Q.; Chen, L. M.; Yi, T. *Chem.—Eur. J.* **2010**, *16*, 9099.
(43) Huang, J. W.; Xu, J. S.; Xu, R. X. *Biomaterials* **2010**, *31*, 1278.
(44) Feng, F.; Mal, A.; Kabo, M.; Wang, J. C.; Bar-Cohen, Y. *J. Acoust. Soc. Am.* **2005**, *117*, 2347.
(45) Hu, J. M.; Liu, S. Y. *Macromolecules* **2010**, *43*, 8315.
(46) Ruiz-Hernandez, E.; Baeza, A.; Vallet-Regi, M. *ACS Nano* **2011**, *5*, 1259.
(47) Aznar, E.; Marcos, M. D.; Martinez-Manez, R.; Sancenon, F.; Soto, J.; Amoros, P.; Guillem, C. *J. Am. Chem. Soc.* **2009**, *131*, 6833.
(48) Fomina, N.; McFearin, C.; Sermsakdi, M.; Edigin, O.; Almutairi, A. *J. Am. Chem. Soc.* **2010**, *132*, 9540.
(49) Koo, H. Y.; Lee, H. J.; Kim, J. K.; Choi, W. S. *J. Mater. Chem.* **2010**, *20*, 3932.
(50) McCoy, C. P.; Brady, C.; Cowley, J. F.; McGlinchey, S. M.; McGoldrick, N.; Kinnear, D. J.; Andrews, G. P.; Jones, D. S. *Expert Opin. Drug Delivery* **2010**, *7*, 605.
(51) Griffin, D. R.; Patterson, J. T.; Kasko, A. M. *Biotechnol. Bioeng.* **2010**, *107*, 1012.
(52) Kasko, A. M.; Wong, D. Y. *Future Med. Chem.* **2010**, *2*, 1669.
(53) Pastine, S. J.; Okawa, D.; Zettl, A.; Frechet, J. M. J. *J. Am. Chem. Soc.* **2009**, *131*, 13586.
(54) Jin, Q. A.; Liu, G. Y.; Ji, J. A. *J. Polym. Sci., Part A: Polym. Chem.* **2010**, *48*, 2855.
(55) Woodcock, J. W.; Wright, R. A. E.; Jiang, X. G.; O'Lenick, T. G.; Zhao, B. *Soft Matter* **2010**, *6*, 3325.
(56) You, J.; Zhang, G. D.; Li, C. *ACS Nano* **2010**, *4*, 1033.
(57) Goodwin, A. P.; Mynar, J. L.; Ma, Y. Z.; Fleming, G. R.; Frechet, J. M. J. *J. Am. Chem. Soc.* **2005**, *127*, 9952.
(58) Jiang, X.; Lavender, C. A.; Woodcock, J. W.; Zhao, B. *Macromolecules* **2008**, *41*, 2632.
(59) He, J.; Tong, X.; Zhao, Y. *Macromolecules* **2009**, *42*, 4845.
(60) Kloxin, A. M.; Kasko, A. M.; Salinas, C. N.; Anseth, K. S. *Science* **2009**, *324*, 59.
(61) Peng, K.; Tomatsu, I.; van den Broek, B.; Cui, C.; Korobko, A. V.; van Noort, J.; Meijer, A. H.; Spaink, H. P.; Kros, A. *Soft Matter* **2011**, *7*, 4881.
(62) Cui, W.; Lu, X.; Cui, K.; Wu, J.; Wei, Y.; Lu, Q. *Nanotechnology* **2011**, *22*, 065702.
(63) Babin, J.; Pelletier, M.; Lepage, M.; Allard, J.-F.; Morris, D.; Zhao, Y. *Angew. Chem.* **2009**, *121*, 3379.
(64) Lee, H.-i.; Wu, W.; Oh, J. K.; Mueller, L.; Sherwood, G.; Peteanu, L.; Kowalewski, T.; Matyjaszewski, K. *Angew. Chem.* **2007**, *119*, 2505.
(65) Goodwin, A. P.; Mynar, J. L.; Ma, Y.; Fleming, G. R.; Frechet, J. M. J. *J. Am. Chem. Soc.* **2005**, *127*, 9952.
(66) Weissleder, R. *Nat. Biotechnol.* **2001**, *19*, 316.
(67) Chen, C. C.; Lin, Y. P.; Wang, C. W.; Tzeng, H. C.; Wu, C. H.; Chen, Y. C.; Chen, C. P.; Chen, L. C.; Wu, Y. C. *J. Am. Chem. Soc.* **2006**, *128*, 3709.
(68) Braun, G. B.; Pallaoro, A.; Wu, G. H.; Missirlis, D.; Zasadzinski, J. A.; Tirrell, M.; Reich, N. O. *ACS Nano* **2009**, *3*, 2007.
(69) *Near-Infrared Applications in Biotechnology*; Raghavachari, R., Ed.; M. Dekker: New York, 2001; Vol. 25.
(70) Watanabe, W.; Arakawa, N.; Matsunaga, S.; Higashi, T.; Fukui, K.; Isobe, K.; Itoh, K. *Opt. Express* **2004**, *12*, 4203.
(71) Aujard, I.; Benbrahim, C.; Gouget, M.; Ruel, O.; Baudin, J. B.; Neveu, P.; Jullien, L. *Chem.—Eur. J.* **2006**, *12*, 6865.
(72) Furuta, T.; Watanabe, T.; Tanabe, S.; Sakyo, J.; Matsuba, C. *Org. Lett.* **2007**, *9*, 4717.
(73) Suzuki, A. Z.; Watanabe, T.; Kawamoto, M.; Nishiyama, K.; Yamashita, H.; Ishii, M.; Iwamura, M.; Furuta, T. *Org. Lett.* **2003**, *5*, 4867.
(74) Furuta, T.; Wang, S. S. H.; Dantzker, J. L.; Dore, T. M.; Bybee, W. J.; Callaway, E. M.; Denk, W.; Tsien, R. Y. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 1193.
(75) Amir, R. J.; Pessah, N.; Shamis, M.; Shabat, D. *Angew. Chem., Int. Ed.* **2003**, *42*, 4494.
(76) Denning, R. G.; Pawlicki, M.; Collins, H. A.; Anderson, H. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 3244.
(77) Sagi, A.; Weinstain, R.; Karton, N.; Shabat, D. *J. Am. Chem. Soc.* **2008**, *130*, 5434.
(78) Weinstain, R.; Sagi, A.; Karton, N.; Shabat, D. *Chem.—Eur. J.* **2008**, *14*, 6857.
(79) Schonle, A.; Hell, S. W. *Opt. Lett.* **1998**, *23*, 325.