Supporting Information

Fast-Photodegradable Block Copolymer Micelles for Burst Release

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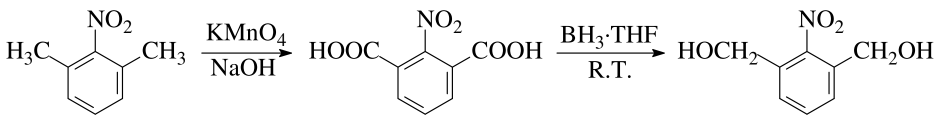
1. Synthesis

Materials. Tetrahydrofuran (THF, 99%) was refluxed with sodium and a small amount of benzophenone and distilled prior to use. 1,3-Dimethyl-2-nitrobenzene (99%), potassium permanganate ($KMnO_4$, ≥99.0%), borane tetrahydrofuran complex solution (1.0 M, in THF), anhydrous *N*,*N*-dimethylformamide (99.8%) and tolylene 2,4-diisocyanate (95%) were purchased from Aldrich and used directly. Poly(ethylene oxide) monomethyl ether (M_n=2000 g/mol) was purchased from Aldrich and dried by azeotropic distillation using anhydrous toluene.

Characterizations. ^{1}H NMR spectra were recorded on a Bruker 300MHz spectrometer using deuterated chloroform as solvent and tetramethylsilane as internal standard. The spectra were used to determine the number-average molecular weights (M_n) of triblock copolymer PEO-*b*-PUNB-*b*-PEO. A Waters size exclusion chromatograph (SEC) instrument, equipped with a Waters 410 differential refractometer detector and a Waters 996 photodiode array detector, was also utilized to measure the M_n, M_w (weight-average molecular weight) and the polydispersity index (PDI) using polystyrene (PS) standards. The SEC measurements were conduced at 35 ^{o}C using one column (Waters Styragel HR4E, 7.8 mm × 300 mm, 5 μm beads) and THF eluent (flow rate: 1.0 mL min^{-1}). UV-vis spectra were recorded with a Varian 50 Bio spectrophotometer. Tapping-mode atomic force microscopy (AFM, Nanoscope IV) was used to examine the BCP micelles solution-cast on mica plate, followed by removing solvent with a filter paper. Dynamic light scattering (DLS) experiments were carried out using a Brookhaven goniometer (BI-200) equipped with an avalanche photodiode detector (Brookhaven, BI-APD), a digital correlator (Brookhaven, TurboCorr) that calculates the photon intensity autocorrelation function $g^2(t)$ and a helium-neon laser (λ = 632.8 nm). The hydrodynamic diameter (D_H) values of the micelles were obtained by a cumulant and CONTIN analysis. The UV irradiation beam was generated by a spot curing system (Novacure 2100) combined with an interference filter for the used 300 nm wavelength (10 nm bandwidth, Oriel), with the beam intensity measured with a powermeter (Oriel).

Synthesis of 2-nitro-1,3-benzenedicarboxylic acid. The synthetic procedure for 2-nitro-1,3-benzenedimethanol is shown in Scheme S1. 2-Nitro-1,3-benzenedicarboxylic acid was firstly synthesized according to a literature method. A stirred mixture of 1,3-dimethyl-2-nitrobenzene (15.8 g, 0.105 mol), water (800 mL) and sodium hydroxide (6.4 g, 0.16 mol) was heated to 95 ºC, then KMnO4 (66 g, 0.418 mol) was added in portions over a period of 3 hrs. The resulting mixture was refluxed for another 20 h, cooled and filtered; the filtrate was acidified with concentrated HCl and the precipitate was collected, dried and its structure was verified by ^{1}H NMR spectroscopy (Figure S1).



Scheme S1. Synthesis for 2-nitro-1,3-benzenedimethanol.

Synthesis of 2-nitro-1,3-benzenedimethanol.

A solution of 2-nitro-1,3-benzenedicarboxylic acid (8.0 g, 38 mmol) in 50 mL anhydrous THF was cooled to 0 °C in the presence of N_2, and then 1.0 M borane-tetrahydrofuran (200 mL) was added dropwise over about 1 h. The reaction mixture was allowed to warm slowly to room temperature and stirred for another 48 h. Methanol (40 mL) was then added into the reaction system slowly by syringe, the mixture filtered and the filtrate evaporated with a rotary evaporator. The residue was redissolved in ethyl acetate and washed with water (3×100 mL). The organic layer was dried with anhydrous $MgSO_4$ overnight before the solvent was removed on a rotary evaporator. The resulting yellow solid was further purified by silica gel chromatography (hexane:ethyl acetate=1:1) to obtain 2-nitro-1,3-benzenedimethanol (4.5 g, 65% yield). Its structure was confirmed by ^1H NMR spectroscopy (Figure S2).

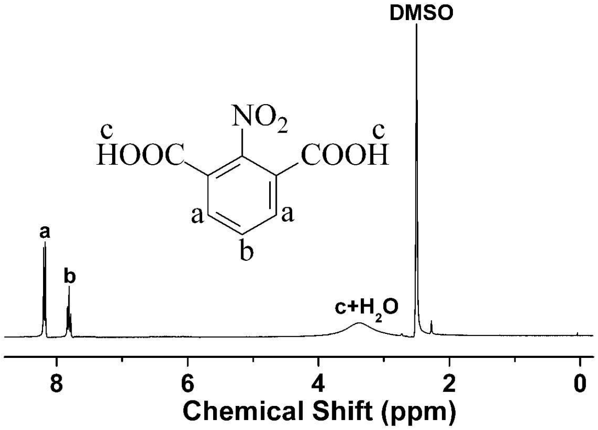


Figure S1. The ^1H NMR spectrum of 2-nitro-1,3-benzenedicarboxylic acid.

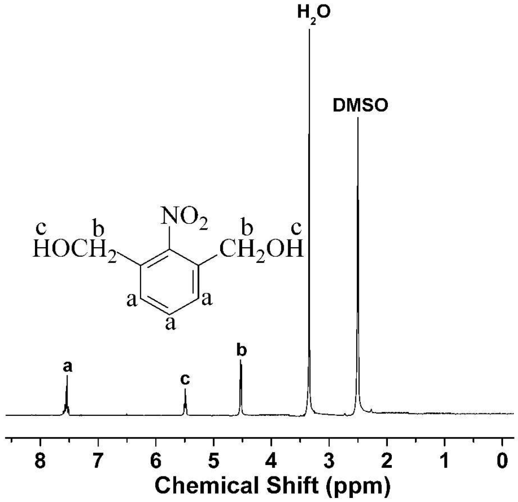


Figure S2. The ^1H NMR spectrum of 2-nitro-1,3-benzenedimethanol.

Synthesis of PEO-*b*-PUNB-*b*-PEO triblock copolymer.

The PEO-*b*-PUNB-*b*-PEO triblock was synthesized via a one-pot procedure. The central PUNB block was obtained by condensation polymerization of 2-nitro-1,3-benzenedimethanol with tolylene 2,4-diisocyanate in slight excess and it was terminated with poly(ethylene oxide) monomethyl ether. The detailed polymerization procedure is as follows. In a 25 mL two-necked flask, 2-nitro-1,3-benzenedimethanol (0.38 g, 2.08 mmol) was dissolved in 4.0 mL of anhydrous DMF in the presence of N_2. The reaction flask was quickly covered with aluminum foil to avoid the sunlight. Tolylene 2,4-diisocyanate (0.39 g, 2.25 mmol) dissolved into 1.0 mL of anhydrous DMF was then added into the flask by syringe in the presence of N_2. The reaction flask was finally immersed into an oil bath thermostated at 50 ^{o}C. After polymerization for 12 h, poly(ethylene oxide) monomethyl ether (0.26 g, 0.13 mmol) dissolved into 2.0 mL of anhydrous DMF was injected into the reaction flask under N_2 and the reaction continued for another 24 h. Afterward, the polymer solution was directly added dropwise into diethyl ether, the polymer precipitated was collected by filtration. The obtained yellow powder was further purified twice by adding its THF solution in diethyl ether for precipitation. After filtration, the lightly yellow PEO-*b*-PUNB-*b*-PEO triblock was collected and dried under vacuum overnight (0.88 g, yield 86%). The triblock copolymer was firstly characterized with size exclusion chromatograph (SEC) with polystyrene (PS) standards and THF eluent in comparison with PEO monomethyl ether, yielding M_n=15100 g/mol and PDI=1.38 as compared to the 2000 g/mol PEO with PDI=1.06. In order to estimate the composition of the triblock copolymer, ^{1}H NMR spectrum was measured and shown in Figure S3. Knowing the molecular weight of PEO, the molecular weight of PEO-*b*-PUNB-*b*-PEO was determined by comparing the integrals of peak *g* at δ=5.20-5.30 ppm (from PUNB) and peak *b* at δ=3.60-3.70 ppm (from PEO), yielding $M_{n,NMR}$=14000 g/mol, the degree of polymerization of PUNB being 28.

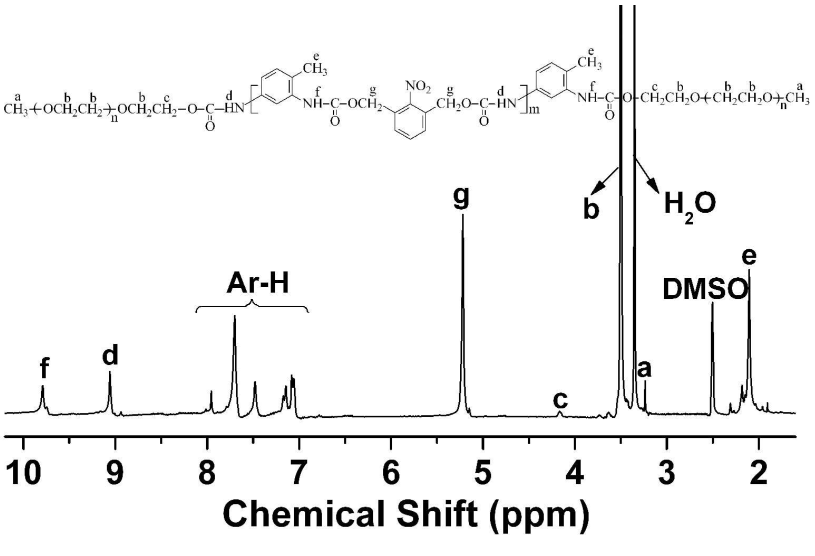


Figure S3. The ^{1}H NMR spectrum of PEO-*b*-PUNB-*b*-PEO triblock copolymer (in DMSO-d6).

2. Photodegradation of PEO-*b*-PUNB-*b*-PEO as Revealed by SEC Measurements

The continuous photodegradation of PEO-*b*-PUNB-*b*-PEO upon UV irradiation was monitored by means of SEC using a THF solution at a high BCP concentration of 10 mg/mL (required for the SEC measurements). The results are shown in Figure S4. As the UV irradiation goes on, more and more species of decreased molecular weights are formed, shifting the elution peaks to longer elution times.

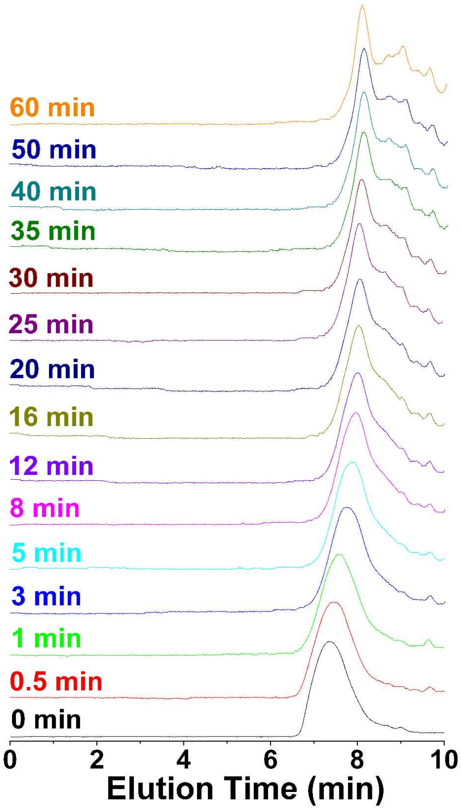


Figure S4. SEC traces of PEO-*b*-PUNB-*b*-PEO in THF (10 mg/mL) recorded as a function of UV irradiation time (300 nm, 50 mW.cm^{-2}).

3. Photoreaction of PEO-*b*-PUNB-*b*-PEO as Revealed by UV-vis Spectra

Figures S5 and S6 show the UV-vis spectra of BCP dissolved in THF and BCP micelles in aqueous solution upon UV irradiation, respectively. In both cases, the spectral changes indicate the photodegradation of the PUNB block. From the BCP design, it is expected that the randomly occurred photocleavage of nitrobenzyl moieties on the main chain could generate species of various sizes and contain nitrosobenzyl and residual nitrobenzyl units. This accounts for the increased absorption over a wide range of wavelengths between ~ 300-500 nm as the photoreaction progresses. It is interesting to notice that due to the large number of nitrobenzyl units on the hydrophobic main chain, it is not necessary to degrade the PUNB block onto small species to break the micelle core. The micelle core can be disintegrated quickly, after a few cleavages on each chain, while the photoreaction continues on all species still bearing nitrobenzyl groups. This explains why the fluorescence quenching of Nile Red can occur shortly upon UV irradiation, while the photoreaction proceeds continuously over a longer period of time.

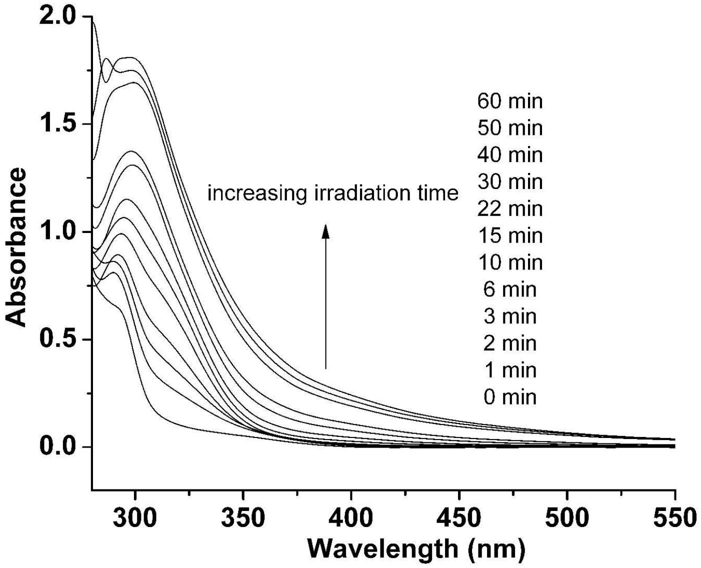


Figure S5. UV-vis spectra of PEO-*b*-PUNB-*b*-PEO dissolved in THF (0.06 mg/mL) and subjected to UV irradiation (300 nm, 50 mW/cm^2, solution volume 3 mL).

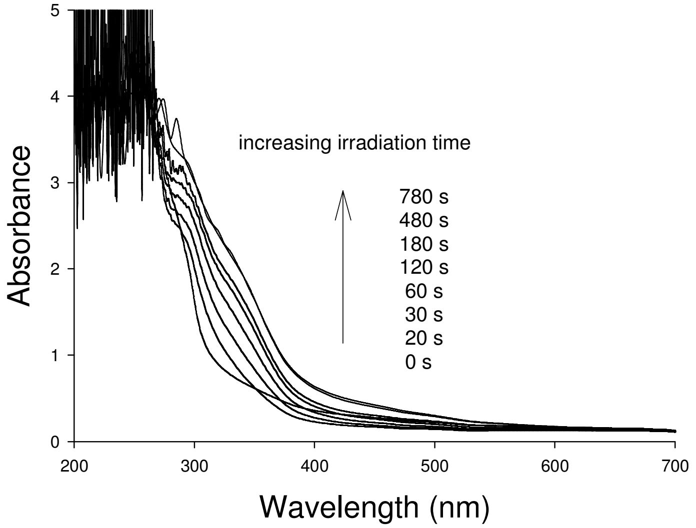


Figure S6. UV-vis spectra of PEO-*b*-PUNB-*b*-PEO micelles in aqueous solution (0.2 mg/mL) and subjected to UV irradiation (300 nm, 250 mW/cm^2, solution volume 0.7 mL).

4. Fluorescence of Nile Red in a THF Solution of PEO-*b*-PUNB-*b*-PEO Subjected to Photodegradation

Figure S7 shows the result of a control test. Nile Red was dissolved with the BCP in either THF or a mixture of THF/water (5:1, v/v), and the solution was subjected to UV irradiation under the same conditions as for Nile Red-loaded BCP micelles in aqueous solution. No fluorescence change was observed after 60 s UV irradiation. This result indicates that photodegraded species could not quench the fluorescence emission of Nile Red.

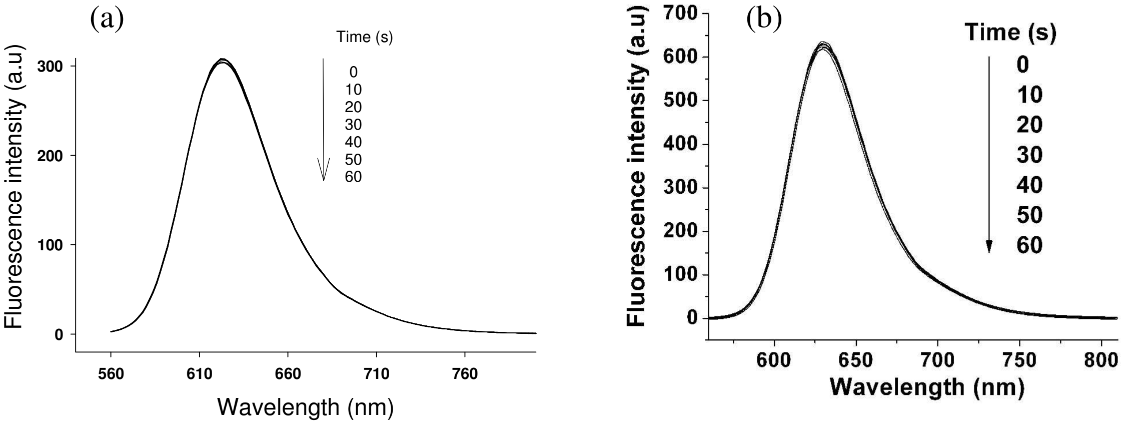


Figure S7. Fluorescence emission spectra (λ_{ex}=550 nm) of Nile Red dissolved with PEO-*b*-PUNB-*b*-PEO (0.2 mg/mL) in (a) THF and (b) THF/water (5:1, v/v) under UV irradiation (300 nm, 250 mW/cm^2, solution volume 0.7 mL).