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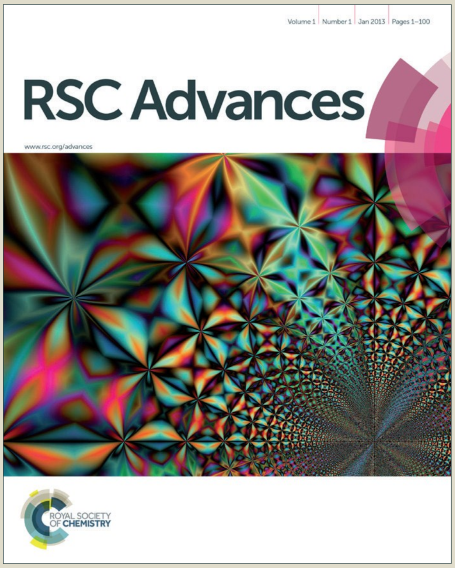

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ARTICLE

Photocleavable Amphiphilic Diblock Copolymer with an Azobenzene Linkage

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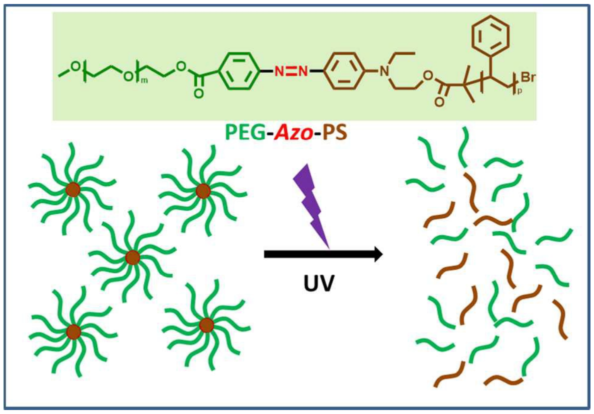
Amphiphilic diblock copolymer with an azobenzene linkage was synthesized by a macromolecular azo coupling reaction between the PEG based macromolecular diazonium salt and PS based polymeric block with functional terminal. Colloidal aggregates could be directly prepared by self-assembly of the prepared amphiphilic copolymer in selective solvents (THF/H_2O). By irradiation with UV light, the azobenzene linkage in the block copolymer can be efficiently photocleaved. Thus, the colloidal aggregates of the amphiphilic diblock copolymer will be disrupted due to the cleavage of the azobenzene junction.

1. Introduction

Block copolymers composed of two or more homopolymer chains linked by covalent bond have been attracted much attention.[1-6] Due to their unique architecture and properties, block copolymers as one of the most important classes of synthetic materials were often used to create nanostructures by self-assembly in bulk or in solution, which can be used as nanoscale templating, nanoscale separations or drug delivery systems and so on.[7-12] Recently, researches have been focused on the smart block copolymers responding to external stimuli, such as temperature, pH, enzyme, gas, light and many others.[13-23] Particularly, photocleavable polymers have received much attention in recent years.[24-27] Light can accurately approach to materials in non-contacting manners. In addition, various types of parameters including light intensity, wavelength, polarization etc can be simply tuned. Such photocleavable polymers can be exactly degraded by photo irradiation, which can be potential used in drug delivery, biomaterials, photodynamic therapeutics and many others. Compared with side chain type photocleavable polymers, the main chain type photocleavable polymers will generate fewer small molecular by-products. Up to date, many efforts have been made to synthesize such block polymers containing the cleavable covalent junction.[28-33] For example, the block polymers can be synthesized by introduce the terminal segment bearing the cleavable covalent bond to one polymer block then followed with various living/controlled polymerization or click reaction with another polymer block. Very recently, we reported a modular strategy for the efficient synthesis of amphiphilic diblock copolymers by macromolecular azo coupling reaction between two polymer blocks.[34-37] It has been reported that azobenzene groups can be photodegraded just by ultraviolet light irradiation.[38] Thus, in our strategy, an azobenzene linkage will naturally generate after the macromolecular azo coupling reaction. It does not need to purposely introduce the cleavable covalent bond to the copolymer any more. Self-assembly of this azobenzene linked copolymer can result uniform colloidal aggregates. By irradiation with ultraviolet light, the cleavage of the azobenzene junction in the copolymer will disrupt the assembly aggregates (Scheme 1).



Scheme 1. Schematic representation of self-assembly aggregates formation from azobenzene linked diblock copolymer, subsequent step of disruption of these aggregates due to the degradation of the azobenzene linkage.

2. Experimental Section

2.1 Materials and characterization

2-(N-Ethylanilino)ethanol (> 97 %) and Poly(ethylene glycol) methyl ether (Mn = 5000, 1900) were received from TCI and Aldrich respectively. *p*-Toluenesulfonyl chloride (99 %, TsCl), 2,2'-Dipyridyl (99 %) and Cuprous Bromide were purchased from J&K Chemical, especially the cuprous bromide were successively purified with glacial acetic acid, ethyl alcohol absolute and anhydrous diethyl ether. Styrene (Acros, 99 %) was distilled to remove the radical inhibitor before utilization. Ultrapure water (resistivity > 18.0

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MΩ·cm) was supplied by a Milli-Q water purification system and used for all experiments. All other solvents and reagents were purchased commercially and used as received. JEOL JNM-ECA 600 spectrometer was used to measure the ^{1}HNMR spectra. A gel permeation chromatography (GPC) apparatus using THF as eluent at a flow rate of 1.0 mL/min at 25 °C was used to measure the number average molecular weights (Mn) and molecular weight distributions (PDI), which was calibrated by using linear polystyrene standards. Photodegradation process was carried out using a 1kW high pressure mercury lamp as a light source. An Agilent 8453 UV-Vis spectrophotometer was used to measure the UV-Vis spectra. Hitachi H-7650B microscope with an accelerating voltage of 80 KV was used to perform the transmission electron microscopy (TEM) observation.

2.2 Synthesis of tosylate ended poly (ethylene glycol) (PEG-Ts)

Poly(ethylene glycol) monomethyl ether (PEG) (Mn = 5000, PDI = 1.10) (15.8 g, 3.16 mmol) and 3 mL triethylamine were dissolved in 50 ml CH_2Cl_2. This solution was cooled in an ice bath. Then 3 g of 4-toluenesulfonylchloride (15.7 mmol) was added. The reaction mixture was kept at 0 °C for 2 h and stirred at room temperature for 12 h. The product was then obtained by precipitated in cold diethyl ether and recrystallized from ethanol twice. PEG-Ts: Mn (GPC) = 6300, PDI = 1.09.

2.3 Synthesis of PEG-NH_2

PEG-Ts (15.3 g, 3 mmol) and p-aminobenzoic acid (1.7 g, 12 mmol) were dissolved in 50 mL DMF. Potassium carbonate (2.1 g) was added into above DMF solution. The reaction mixture was kept at 60 °C for 24 h with stirring. Most DMF was removed by vacuum evaporation. Then 60 mL ice water was added to above mixture. The solution was extracted with CH_2Cl_2 and washed with ice water. After dried with anhydrous $MgSO_4$ and vacuumed to remove most of the solvent, the mixture was poured into an excessive amount of cold diethyl ether. The final product was collected by filtration. Yield: 70%. Mn (GPC) = 6300, and PDI = 1.08.

2.4 Synthesis of PS with anilino functionality in the end of the polymer chain (PS-N-Ph)

CuBr (35.9 mg, 0.25 mmol) and 2,2-dipyridyl (78.1 mg, 0.5 mmol) were added to a Schlenk flask. Then it was degassed and back-filled with argon three times. Following this step, deoxygenated ATRP initiator (41 mg, 0.13 mmol) and styrene 5 mL were added via gas-tight syringes which had been previously purged with argon. After degassing by three freeze–pump–thaw cycles, the flask was immersed in an oil bath preheated to 110 ^{o}C. After the polymerization for 4 h, the reaction mixture was diluted with THF and passed through an alumina column to remove catalyst. The filtrate was concentrated and poured into an excess amount of methanol. The precipitate was collected by filtration, washed with methanol and then dried in a vacuum oven for 24 h. Mn (GPC) = 13000, and PDI = 1.20.

2.4 Synthesis of azobenzene linked diblock copolymer (PEG-*Azo*-PS)

The amphiphilic diblock copolymer with an azobenzene linkage was synthesized by the macromolecular azo coupling reaction between PEG based macromolecular diazonium salt and PS based polymeric block with functional terminal. PS-N-Ph (130 mg, 0.01 mmol) was dissolved in 50 mL DMF at 0 ^{o}C. The diazonium salt of PEG-NH_2 was prepared by adding an aqueous solution of sodium nitrite (3 mg in 0.3 mL of water) into a mixture of PEG-NH_2 (102 mg, 0.02 mmol), HCl (36%, 0.03 mL) and H_2O (0.4mL) at 0 ^{o}C. The mixture was stirred at 15 min at that temperature and then was added dropwise into above DMF solution. Then the reaction was kept at 0 ^{o}C for 72 h. Then the solution was precipitated with plenty of water. The precipitate was collected by filtration and dried in a vacuum oven for 72 h. Mn (GPC) = 18000, and PDI = 1.22.

2.5 Synthesis of diblock copolymer (PEG-*b*-PS) without azobenzene linkage

Macromolecular ATRP initiator PEG-Br was prepared by the esterification reaction between poly(ethylene glycol) methyl ether (Mn = 1900) and 2-bromoisobutyryl bromide in dry CH_2Cl_2.[39] CuBr (28.7 mg, 0.2 mmol) and 2,2-dipyridyl (62.5 mg, 0.4 mmol) were added to a Schlenk flask. Then it was degassed and back-filled with argon three times. Following this step, deoxygenated PEG-Br (206.5 mg, 0.1 mmol) and styrene (2.5 ml, 21.8 mmol) were added via gas-tight syringes which had been previously purged with argon. After degassing by three freeze–pump–thaw cycles, the flask was immersed in an oil bath preheated to 110 ^{o}C. After the polymerization for 3.0 h, the reaction mixture was diluted with THF and passed through an alumina column to remove catalyst. The filtrate was concentrated and poured into an excess amount of methanol. The precipitate was collected by filtration, washed with methanol and then dried in a vacuum oven for 24 h. Mn (GPC) = 11600, and PDI = 1.14.

2.6 Self-assembly of PEG-*Azo*-PS

PEG-*Azo*-PS (4.0 mg) was dissolved in anhydrous THF (1.0 mL), which is a good solvent for both PEG and PS blocks. To prepare the self-assembly aggregates, the THF solution was added dropwise into ultrapure water (4.0 mL), which is a good solvent for the PEG block but not for the PS block. The polymer solutions were gently stirred during the addition. The final solution was then dialyzed against deionized water for 48 hours to remove THF.

2.7 Photodegradation of PEG-*Azo*-PS

Suitable amounts of PEG-*Azo*-PS samples were dissolved in THF to yield homogeneous solutions with the concentration at 3.0×10^{-5} M for UV analysis. Then the solutions were irradiated with high pressure mercury lamp (1kW) every 150 seconds until the absorption no longer changes. The colloidal aggregates of PEG-*Azo*-PS in ultrapure water were irradiated with the high pressure mercury lamp for about 20 min. The white solid precipitation was then isolated by centrifugation and the corresponding supernatant was evaporated and vacuum dried for further GPC and ^{1}H NMR analyses.

3. Results and discussion

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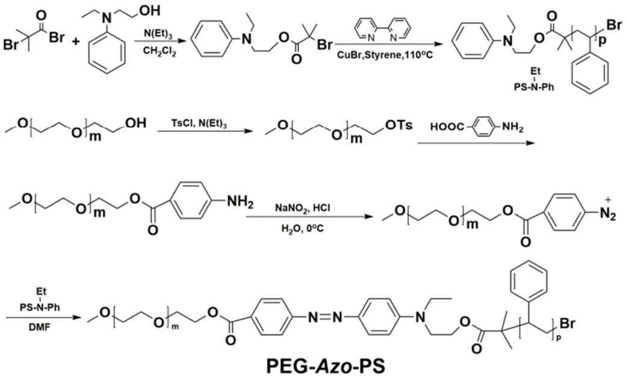

Scheme 2 Synthetic route of amphiphilic diblock copolymer PEG-*Azo*-PS through macromolecular azo coupling reaction.

The azobenzene linked amphiphilic diblock copolymer (PEG-*Azo*-PS) was synthesized in a manner similar to that reported previously (Scheme 2).[37] Aniline-functionalized PEG was prepared by substitution reaction between the tosylate ended PEG and *p*-aminobenzoic acid. The hydrophilic block with diazonium salt group was obtained by the diazotization of above aniline-functionalized PEG. The hydrophobic block with terminal suitable for azo-coupling reaction was obtained by ATRP method. Then the diblock copolymer was prepared through macromolecular azo coupling reactions between the above mentioned two polymeric blocks.

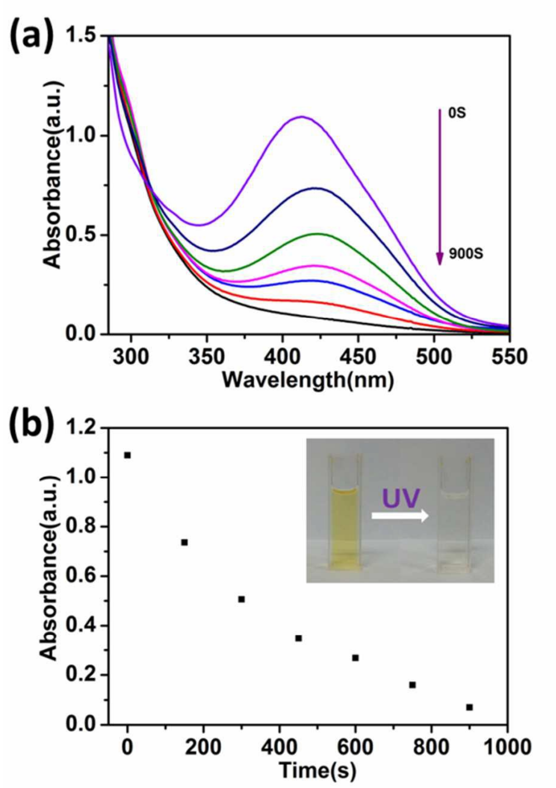

Figure 1. UV/Vis absorption spectra of amphiphilic diblock copolymer (PEG-*Azo*-PS) in THF solution (3.0×10^{-5} M) upon irradiation with UV light (a) and (b) shows the absorption intensity at 427 nm as a function of irradiation time. The insert shows the photographs of polymer solution before and after treating with UV light irradiation.

The photo cleavage of the azobenzene linked amphiphilic diblock copolymer was studied by using UV-Vis spectra. Figure 1 gives the UV-Vis spectra of PEG-*Azo*-PS THF solution upon irradiation with of UV light (1 kW high pressure mercury lamp). Before irradiation of UV light, the curve shows typical absorption behavior of the pseudo-stilbene type of azo chromophores, the maximum absorbance of PEG-*Azo*-PS in THF appears at 427 nm, which is related to the π-π* transition of the trans isomers of the azobenzene units. After irradiation with UV light, this peak at 427 nm gradually decreased. The relationship between the maximum absorbance of the azobenzene linked diblock copolymer and the irradiation time is showed in Figure 1(b). It can be found that the λ_{max} decreased with the irradiation time. After about 15 min irradiation with UV light, the absorbance at 427 nm almost decreased to zero, which indicated the photo cleavage of the azobenzene linkage. From the photo image of the PEG-*Azo*-PS THF solution, it can be found that the color of the solution has changed from orange to colorless after the UV light irradiation. Anyway, it should be pointed out that the well-known photochromic azobenzene group will show obviously photoisomerization behavior instead of photodegradation upon irradiation with an appropriate wavelength matched the absorption band, which has been shown in Figure S7.

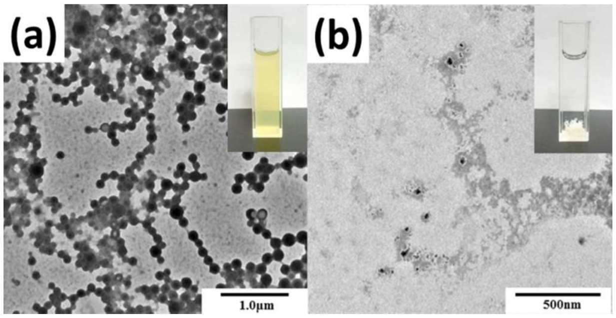

Figure 2. Typical TEM images of the self-assembly aggregates of the diblock copolymer PEG-*Azo*-PS before and after the UV light irradiation.

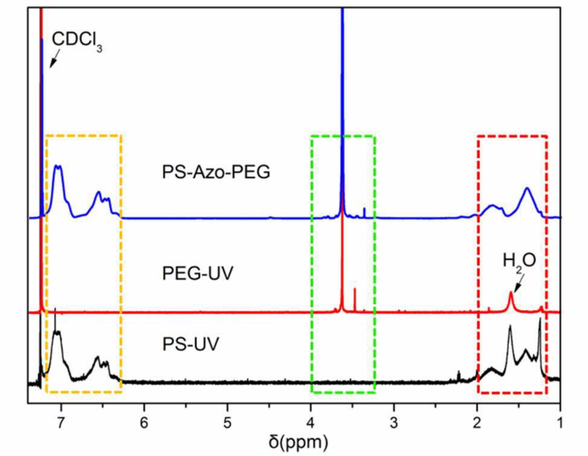

Figure 3. ^{1}H NMR spectra (600 MHz, $CDCl_3$, 298 K) of PS-*Azo*-PEG, PEG-UV and PS-UV.

The self-assembly aggregates of the PEG-*Azo*-PS were prepared in selected solvents. 1000 μL PEG-*Azo*-PS THF

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solution (4.0 mg/mL) was added dropwise into 10 mL of deionized water under stirring. The dispersions were then dialyzed against deionized water for 48 hours to remove THF before further measurements. TEM image of aggregates of the azobenzene linked block copolymer is showed in Figure 2a. It can be found that spherical structures have been formed by hydrophobic aggregation of the polymeric chains in a THF-H_2O dispersion medium. The size of the aggregates is about 60-80 nm. Treatment with the UV light irradiation, the yellow polymer suspension turned colorless and a white solid appeared (Inserts of Figure 2). The aggregates could be photo triggered disruption, which was confirmed by TEM (Figure 2b). The spherical self-assembly aggregates could no longer be observed after the UV light irradiation.

The white solid precipitation was isolated by centrifugation to give the PS part (PS-UV). After removal of the white solid, the obtained aqueous solution was vacuum dried to give the PEG part (PEG-UV). The resulted polymer segments were examined with ^{1}H NMR spectroscopy (Figure 3). Compared with PS-*Azo*-PEG, the peaks in the aromatic protons regions (7.20-6.86 ppm, 6.75-6.28 ppm) and in high magnetic field (1.98-1.20 ppm) are totally disappeared in PEG part. At the same time, the characteristic peaks at 3.72-3.58 ppm are also disappeared in PS part, illustrating the efficient degradation of the copolymer after treating with UV light.

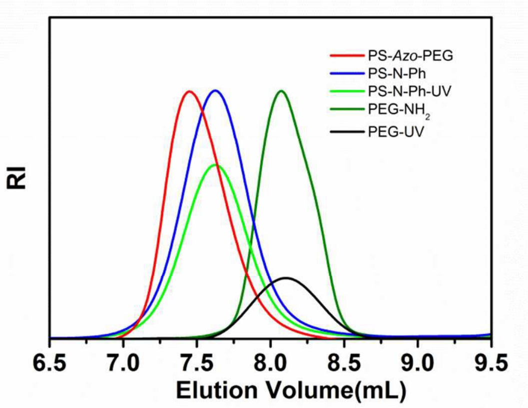

Figure 4. GPC traces of aniline functionalized PEG (PEG-NH$_2$), terminal-functionalized PS (PS-N-Ph), diblock copolymer PEG-*Azo*-PS and the obtained PEG-UV and PS-UV after the UV light irradiation.

The GPC measurements were used to verify above photo cleavable property of the azobenzene linkage in this diblock copolymer. Figure 4 shows the traces of aniline-functionalized PEG (PEG-NH$_2$), functionalized PS block (PS-N-Ph), the coupled diblock copolymer (PEG-*Azo*-PS), photo cleaved PS and PEG parts (PS-UV and PEG-UV). The calculated molecular weights from GPC of PEG-NH$_2$, PS-N-Ph, PEG-*Azo*-PS, PS-UV and PEG-UV are 6300, 13000, 18000, 13000 and 6000, respectively. It can be seen that the photo cleaved result polymers exhibit similar retention times as the initial aniline-functionalized PEG (PEG-NH$_2$) and functionalized PS block (PS-N-Ph). For comparison, the PEG-*b*-PS prepared by ATRP method was used to measure the GPC data after the same UV irradiation. The only difference between the PEG-*Azo*-PS and PEG-*b*-PS is the azobenzene linkage. It can be found that the GPC trace of the PEG-*b*-PS without azobenze linkage is same before and after the UV irradiation (Figure 5). The above GPC results also confirm the photo cleavage of the azobenzene linkage.

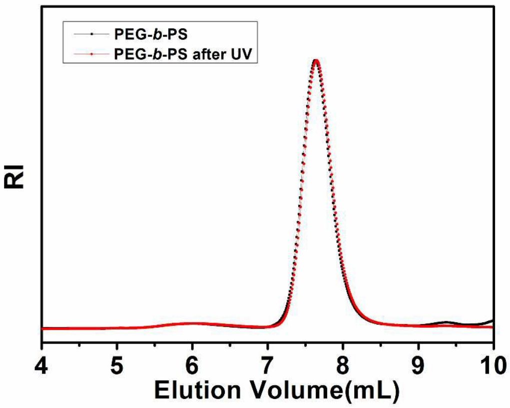

Figure 5. GPC traces of diblock copolymer PEG-*b*-PS without azobenzene linkage before and after the UV light irradiation.

The photo controlled release experiments were carried on by using pyrene as a model molecule (Figure S8). It can be seen that the intense fluorescence was detected in the polymer colloidal aggregates loading pyrene, while little fluorescence was found in the absence of polymer aggregates since the hydrophobic pyrene could hardly be dissolved in water (Figure S8a). The fluorescence of the mixture decreased with increasing UV irradiation time were shown in Figure S8b. After UV irradiation for 24 min, most of the loaded molecules could be released since the hydrophobic core of the colloidal aggregates disappeared because of its photo-cleavage.

Conclusions

In conclusion, we have reported the photocleavage of amphiphilic diblock copolymer with an azobenzene linkage, which was synthesized by a macromolecular azo coupling reaction. The azobenzene linkage will naturally generate after the macromolecular azo coupling reaction. This kind of amphiphilic diblock copolymer could self-assemble into colloidal sphere nanostructures. Treatment with UV light irradiation, the self-assembly aggregates of the amphiphilic diblock copolymer will be disrupted due to the cleavage of the azobenzene junction, which endowed the self-assembly nanostructures with a controlled release of encapsulated molecules.

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References

1. S. Strandman, X. Zhu, *Prog. Polym. Sci.*, **2015**, *42*, 154-176.
2. C. Boyer, N. A. Corrigan, K. Jung, D. Nguyen, T.-K. Nguyen, N. N. M. Adnan, S. Oliver, S. Shanmugam, J. Yeow, *Chem. Rev.*, **2016**, *116*, 1803-1949.
3. C. C. Ho, S. J. Wu, S. H. Lin, S. B. Darling, W. F. Su, *Macromol. Rapid Commun.*, **2015**, *36*, 1329-1335.
4. H. Yu, *J. Mater. Chem. C*, **2014**, *2*, 3047-3054.
5. C. Zhang, D. Wang, J. He, M. Liu, G.-H. Hu, Z.-M. Dang, *Polym. Chem.*, **2014**, *5*, 2513-2520.
6. Y. Zha, H. D. Thaker, R. R. Maddikeri, S. P. Gido, M. T. Tuominen, G. N. Tew, *J. Am. Chem. Soc.*, **2012**, *134*, 14534-14541.
7. N. Kamaly, B. Yameen, J. Wu, O. C. Farokhzad, *Chem. Rev.*, **2016**, *116*, 2602-2663.
8. D.-P. Song, Y. Lin, Y. Gai, N. S. Colella, C. Li, X.-H. Liu, S. Gido, J. J. Watkins, *J. Am. Chem. Soc.*, **2015**, *137*, 3771-3774.
9. Z. Ge, S. Liu, *Chem. Soc. Rev.*, **2013**, *42*, 7289-7325.
10. B. Kutikov, J. Song, *ACS Biomater. Sci. Eng.*, **2015**, *1*, 463-480.
11. H. Ahn, S. Park, S.-W. Kim, P. J. Yoo, D. Y. Ryu, T. P. Russell, *ACS Nano*, **2014**, *8*, 11745-11752.
12. L. Ren, C. G. Hardy, C. Tang, *J. Am. Chem. Soc.*, **2010**, *132*, 8874-8875.
13. A. Feng, C. Zhan, Q. Yan, B. Liu, J. Yuan, *Chem. Commun.*, **2014**, *50*, 8958-8961.
14. H. Mori, I. Kato, T. Endo, *Macromolecules*, **2009**, *42*, 4985-4992.
15. Z.-P. Yu, C.-H. Ma, Q. Wang, N. Liu, J. Yin, Z.-Q. Wu, *Macromolecules*, **2016**, *49*, 1180-1190.
16. F. Schacher, T. Rudolph, F. Wieberger, M. Ulbricht, A. H. Muller, *ACS Appl. Mater. Interfaces*, **2009**, *1*, 1492-1503.
17. J. Dong, Y. Wang, J. Zhang, X. Zhan, S. Zhu, H. Yang, G. Wang, *Soft Matte*r, **2013**, *9*, 370-373.
18. J.-F. Gohy, Y. Zhao, *Chem. Soc. Rev.*, **2013**, *42*, 7117-7129.
19. N. Feng, J. Dong, G. Han, G. Wang, *Macromol. Rapid Commun.*, **2014**, *35*, 721-726.
20. W. Wang, Y. Huang, S. Zhao, T. Shao, Y. Cheng, *Chem. Commun.*, **2013**, *49*, 2234-2236.
21. J. Rao, A. Khan, *J. Am. Chem. Soc.*, **2013**, *135*, 14056-14059.
22. H. Yu, *Prog. Polym. Sci.*, **2014**, 39, 781.
23. Y. Zhao, *Macromolecules*, **2012**, *45*, 3647-3657.
24. Y. Gao, H. Qiu, H. Zhou, X. Li, R. Harniman, M. A. Winnik, I. Manners, *J. Am. Chem. Soc.*, **2015**, *137*, 2203-2206.
25. H. Zhao, W. Gu, E. Sterner, T. P. Russell, E. B. Coughlin, P. Theato, *Macromolecules*, **2011**, *44*, 6433-6440.
26. J.-M. Schumers, J.-F. Gohy, C.-A. Fustin, *Polym. Chem.*, **2010**, *1*, 161-163.
27. E. Cabane, V. Malinova, W. Meier, Macromol. *Chem. Phys.*, **2010**, *211*, 1847-1856.
28. J. Xuan, D. Han, H. Xia, Y. Zhao, *Langmuir*, **2013**, *30*, 410-417.
29. M. Rabnawaz, G. Liu, *Macromolecules*, **2014**, *47*, 5115-5123.
30. M. Kang, B. Moon, *Macromolecules*, **2008**, *42*, 455-458.
31. Q. Yan, D. Han, Y. Zhao, *Polym. Chem.*, **2013**, *4*, 5026-5037.
32. M. Tian, R. Cheng, J. Zhang, Z. Liu, Zh. Liu, J. Jiang, *Langmuir*, **2016**, *32*, 12-18.
33. H.Yang,L. Jia, Z. Wang,A. Di-Cicco,D. Levy, P. Keller, *Macromolecules*, **2011**, *44*, 159-165.
34. Y. He, W. He, D. Liu, T. Gu, R. Wei, X. Wang, *Polym. Chem.* **2013**, *4*, 402-406.
35. J. Wang, Y. Zhou, X. Wang, Y. He, *RSC Adv.*, **2015**, *5*, 9476-9481.
36. R. Wei, X. Wang, Y. He, *Eur. Polym. J.*, **2015**, *69*, 584-591.
37. Y. He, W. He, R. Wei, Z. Chen, X. Wang, *Chem. Commun.*, **2012**, *48*, 1036-1038.
38. T. A. Singleton, I. B. Burgess, B. A. Nerger, A. Goulet-Hanssens, N. Koay, C. J. Barrett, J. Aizenberg, *Soft matter*, **2014**, 10, 1325-1328.
39. D. Wang, G. Ye, Y. Zhu, X. Wang, *Macromolecules*, **2009**, 42, 2651-2657.

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Graphical Abstract

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Diblock copolymer with an azobenzene linkage synthesized by a macromolecular azo coupling reaction can be efficiently photocleaved upon UV light irradiation. Thus, the colloidal aggregates of this kind of amphiphilic diblock copolymer will be disrupted due to the cleavage of the azobenzene junction.