# Photocontrollable block copolymer micelles: what can we control?

## Yue Zhao*

Recent progress in the design and development of photocontrollable block copolymer (BCP) micelles is reviewed. By choosing an appropriate photoreaction of photochromic moieties linked to BCPs, such as photoisomerization, photocleavage and photodimerization, various types of control over polymer micelles can be achieved using light. These include either reversible or irreversible dissociation, reversible cross-linking, and reversible morphological transition of polymer micelles in response to light exposure. The design rationale for light-responsive BCPs, the underlying mechanisms of their photocontrol and the possible future development in exploring light as a powerful stimulus to control the structures or functions of BCP micelles are discussed.

## 1.   Introduction

Polymer micelles are generally formed through self-assembly of block copolymers (BCPs) in a block-selective solvent. In aqueous solution, amphiphilic diblock copolymers can form stable micelles with a compact core of the insoluble hydrophobic block and a dispersed corona of the soluble hydrophilic block. Over the last decade or so, research on polymer micelles capable of reacting to environmental changes or external stimuli has been increasingly active. The sustained interest stems from the potential use of stimuli-responsive polymer micelles in controlled delivery applications.[1–5] From the literature it is easy to notice that most efforts have been dedicated to systems that respond to changes in pH[6–9] or in temperature.[10–12] Excellent reviews are available for pH- and thermosensitive polymer micelles.[13–15]

*Département de chimie, Université de Sherbrooke, Sherbrooke, Québec, Canada J1K 2R1. E-mail: yue.zhao@usherbrooke.ca; Fax: +1 819 8218017; Tel: +1 819 8217090*

*Yue Zhao received his BS degree in 1982 from the Chengdu University of Science and Technology in China. He went to France in 1983 and studied at École Supérieure de Physique et de Chimie de Paris with Prof. Lucien Monnerie. After obtaining his PhD in 1987, he did a post-doctoral study with Prof. Robert Prud'homme at Laval University in Canada. In 1991, he joined the Chemistry Department of the University of Sherbrooke and has been a full*

**Yue Zhao**

*professor since 2000. His current research focuses on the design, synthesis and study of stimuli-responsive, self-assembled and nanostructured polymer and liquid crystal materials.*

Quite surprisingly, although light has long been recognized as an external stimulus and used for small-molecule (surfactant-type) micelles,[16–20] it had not really been exploited for polymer micelles until recently. Since the demonstration of the first photocontrollable BCP micelle in 2004,[21] there has been growing interest in designing and developing polymer micelles whose aggregation states and functions can be controlled by light. This feature article focuses mainly on photocontrollable BCP micelles, highlighting the recent progress, discussing the design rationale and the current understanding of the underlying mechanisms, and sharing ideas for possible new developments. Not included are small-molecule photoactive surfactants[16–20] and the use of light to activate the functions of biologically active compounds.[22] As compared to other stimuli, the use of light to trigger a desired reaction of polymer micelles enables more temporal and positional control. We hope to show that by combining the rich polymer chemistry and the chemistry of photochromic molecules, there are still many opportunities for exciting developments on photocontrollable polymer micelles!

## 2.   Reversible dissociation and formation

In order to control polymer micelles using light, they obviously must be light-responsive. To make them light-responsive, a chromophore needs to be incorporated into their structure. In the context of controlled delivery of drugs or other bioagents, an appealing control over polymer micelles is to use light to dissociate them to allow the release of encapsulated molecules at a chosen time and a chosen location. Fig. 1 schematically illustrates the general approach of designing a diblock copolymer whose micelles can be reversibly dissociated and formed upon illumination at two different wavelengths ($\lambda_1$ and $\lambda_2$): one block contains a photochromic moiety in the pendant group, which can be photoswitched between two isomers that can change the block's solubility in a given solvent. For amphiphilic diblock copolymers, the hydrophobic block should bear the photochromic groups and form the micelle core with one isomeric form (the more stable one). Upon absorption of photons at $\lambda_1$, the photochromic groups should be converted to an isomeric form

This journal is © The Royal Society of Chemistry 2009

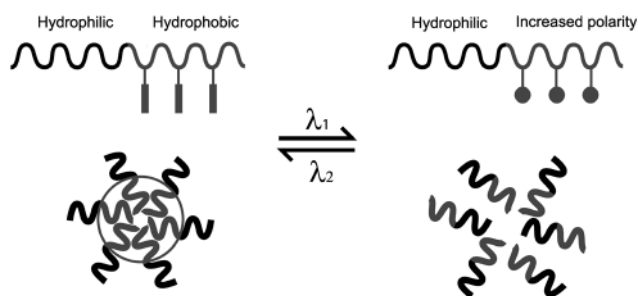*J. Mater. Chem.*, 2009, **19**, 4887–4895 | 4887

**Fig. 1** Schematic illustration of block copolymer micelles that can be reversibly dissociated and formed upon absorption of photons of two different wavelengths. The process is controlled by a reversible photo-isomerization reaction of photochromic groups between two isomeric forms of different polarities.



**Fig. 2** (A) Chemical structure and the photoreaction of an azobenzene-containing diblock copolymer. The hydrophobic block can be reversibly switched between low and high polarity by exposure to UV and visible light as a result of the trans-cis photoisomerization of azobenzene groups. (B) Changes in transmittance for a vesicle solution (in dioxane/water) illuminated with UV (360 nm) and then visible light (440 nm), showing the reversible dissociation and formation of micellar aggregates. SEM images recorded on samples cast from the solution before UV, after UV and after subsequent visible light irradiation confirm the photocontrolled process. Adapted with permission from ref. 23.

that increases significantly the polarity of the hydrophobic block to shift the hydrophilic-hydrophobic balance towards the destabilization of the micelles. The reverse isomerization upon absorption of photons at $\lambda_2$ brings the photochromic groups back to the initial isomeric form and the restored hydrophilic-hydrophobic balance allows micelles to be reformed. Note that only the aggregate in the form of a core-shell micelle is used in the illustration and the discussion for the sake of simplicity. But the rational polymer design and the mechanisms of photocontrol can be applied to other forms of micellar aggregates such as vesicles for which the hydrophobic block constitutes the membrane of the capsules.

The approach depicted in Fig. 1 was first demonstrated by our group using a diblock copolymer containing azobenzene that can be photoswitched between the trans and cis forms upon UV and visible light irradiation.[21,23] As shown in Fig. 2, its hydrophilic block is a random copolymer of poly(*tert*-butyl acrylate-*co*-acrylic acid) [P(*t*BA-*co*-AA)], while the hydrophobic block is a polymethacrylate bearing the azobenzene chromophore (PAzoMA). (Note that all chemical structures are drawn to show the polymer blocks, with the end and connecting groups omitted.) With azobenzene in the trans form, the polymer can form core-shell micelles or vesicles depending on the preparation conditions. Those micellar aggregates display photocontrollable dissociation and formation as a result of the reversible photo-isomerization of azobenzene. Upon illumination of a micellar solution with UV light (360 nm), trans azobenzene groups are converted to the cis isomer, which results in a large increase in the polarity of PAzoMA. Indeed, due to the almost symmetrical structure of the used azobenzene moiety, the trans form has a near zero dipole moment (no charge separation), while the bent cis form has a dipole moment of ~4.4 D according to a density functional theory calculation.[23] This means that when a micellar solution of P(*t*BA-*co*-AA)-*b*-PAzoMA is exposed to UV light, the polarity of the PAzoMA block rises significantly, as the hydrophobic block is no longer hydrophobic enough to preserve the micellar association, micelles are dissociated. But when visible light (440 nm) is subsequently applied to the solution with dissolved BCP chains, the reverse cis-trans isomerization takes place. As azobenzene moieties on the PAzoMA block are recovered to the trans form, micelles are reformed. This photo-controlled reversible process was confirmed unambiguously
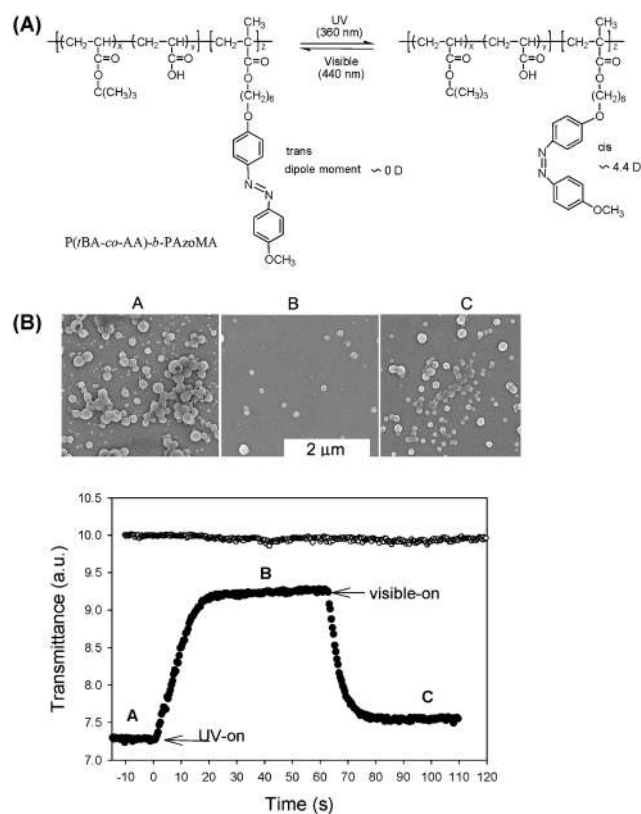
using a sample of P(*t*BA$_{46}$-*co*-AA$_{22}$)-*b*-PAzoMA$_{74}$, as can be seen from the example result in Fig. 2. Upon application of a UV light (360 nm, 18 mW cm$^{-2}$) to a dioxane/water solution of vesicles (~1.5 mL), the optical transmittance of a probe light (633 nm) started to rise, indicating the dissociation of vesicles. When the irradiation was switched to visible light (440 nm, 24 mW cm$^{-2}$), the opposite process occurred immediately; the transmittance dropped as a result of the reformation of the aggregates. From a control test, the higher and essentially unchanged transmittance was obtained with the BCP dissolved in dioxane (no micellar aggregates) and subjected to exactly the same UV and visible light irradiation for the reversible trans-cis photo-isomerization of azobenzene moieties on the dissolved block copolymer. Scanning electron microscope (SEM) observations made on samples cast from the vesicular solution before UV irradiation (marked by A), after 40 s UV irradiation (B) and after 40 s visible irradiation (C), corroborated the changes in transmittance accompanying the reversible photocontrolled process.

On the basis of the revealed mechanism, it is clear that in principle, all photochromic molecules photoswitchable between two isomeric forms having a significant difference in polarity can
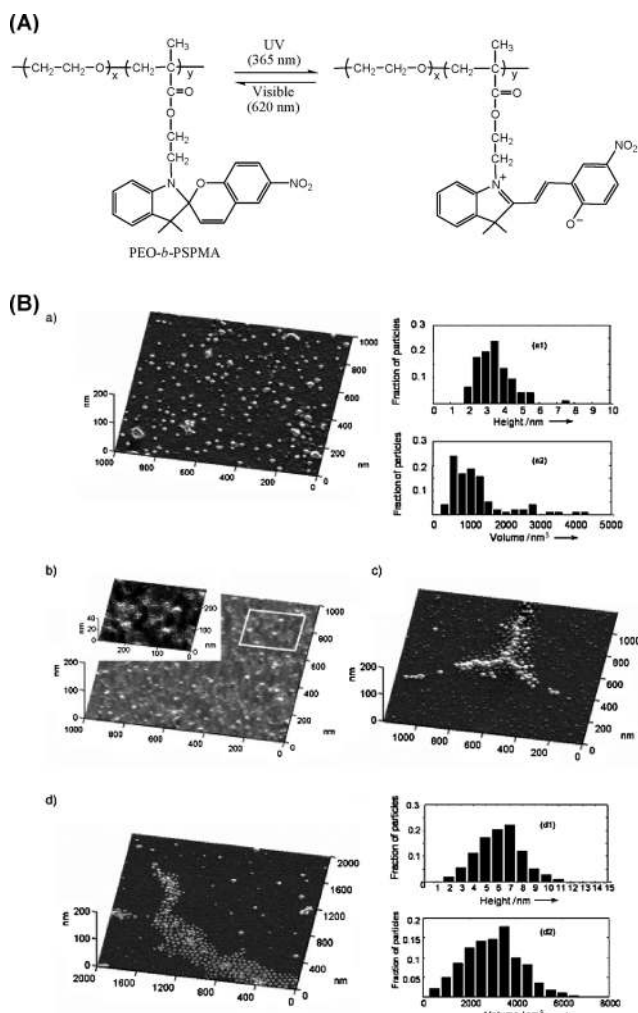
**Fig. 3** (A) Chemical structure and the photoreaction of a spiropyran-containing amphiphilic diblock copolymer. The reversible photo-isomerization between hydrophobic spiropyran (SP) and hydrophilic merocyanine (ME) upon UV and visible light irradiation is responsible for the reversible dissociation and formation of micelles in aqueous solution. (B) AFM images for a micellar solution spin-coated on mica: a) before UV irradiation (a1 and a2 are height and volume distributions of micellar aggregates, respectively), b) after 30 min UV exposure (365 nm), c) after subsequent visible light (620 nm) exposure for 30 min, and d) for 120 min (d1 and d2 are height and volume distributions of reformed micellar aggregates, respectively). Adapted with permission from ref. 24.

be applied to design BCPs whose micelles can be reversibly dissociated and formed by light. Lee et al. reported BCP micelles undergoing such a reversible process in aqueous solution by making use of the reversible photoisomerization between spiropyran and merocyanine.[24] As depicted in Fig. 3, their BCP is composed of poly(ethylene oxide) (PEO) as the hydrophilic block and a polymethacrylate bearing spiropyran moieties as the hydrophobic block (PSPMA). With the hydrophobic spiropyran pendant groups, the BCP can form micelles with the PSPMA core. Upon UV irradiation (365 nm), spiropyran is isomerized to charged merocyanine, which increases the polarity of the poly-methacrylate block and leads to the dissociation of the micelles. With subsequent visible light exposure (620 nm), merocyanine is

converted back to spiropyran and polymer micelles are formed. The AFM images and height and volume distributions in Fig. 3, obtained with a sample of $PEO_{120}$-$b$-$PSPMA_8$, confirmed the photocontrolled micellar dissociation and formation. Micelles were clearly visible before UV irradiation (image a), disappeared after 30 min of UV exposure (image b) and reappeared following subsequent visible light exposure (images c and d for 30 and 60 min of irradiation respectively). The authors also showed that an encapsulated hydrophobic dye (Coumarin 102) could be released during the micellar dissociation under UV irradiation, while part of dye molecules could be re-entrapped by micelles reformed upon visible light exposure.

As compared to the trans-cis isomerization of azobenzene, the conversion of spiropyran to charged merocyanine induces a larger increase in polarity for the hydrophobic micelle core-forming block. Although the polarity change is not the sole factor controlling the dissociation process, a large increase in polarity can be the key to shift the hydrophilic-hydrophobic balance and to trigger the photocontrolled process. For some photochromic molecules, the substitution pattern can be crucial. This is the case for azobenzene. In contrast to the azobenzene moiety used in the BCP discussed with Fig. 2, if azobenzene is para-substituted with an electron-donor and an electron-acceptor group,[25,26] the stable trans form actually has a greater dipole moment than the cis form. This means that upon UV or visible irradiation, the trans-cis isomerization would result in a decrease in polarity for the hydrophobic block, making the dissociation of BCP micelles unlikely to occur.

## 3. Irreversible dissociation

On the basis of the same principal of using light to shift the hydrophilic-hydrophobic balance towards the micellar dissociation, probably more photochromic molecules can be used to design BCPs whose micelles dissociate irreversibly as a result of the photoreaction. The reversibility of micellar dissociation and formation using bistable photoswitches is interesting but unnecessary for controlled delivery applications. To achieve irreversible photocontrolled dissociation of BCP micelles, the photoreaction of the used chromophore should result in a permanent structural change for the hydrophobic block that triggers the process. As schematically depicted in Fig. 4, this can be accomplished through a photoinduced cleavage reaction of
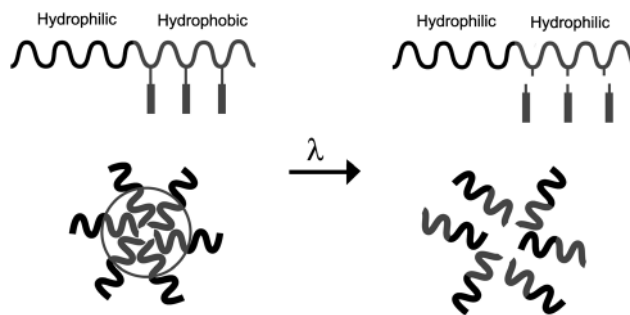


**Fig. 4** Schematic illustration of block copolymer micelles that can be irreversibly dissociated upon exposure to light. The process is controlled by a photocleavage reaction of photochromic groups that transforms the hydrophobic block into a hydrophilic one.

This journal is © The Royal Society of Chemistry 2009

J. Mater. Chem., 2009, **19**, 4887–4895 | 4889

pendant photochromic groups that transforms the hydrophobic block into a hydrophilic one. It is easy to understand the dissociation of micelles when the initially amphiphilic BCP becomes a double-hydrophilic BCP.

The required photoinduced cleavage reaction is possible by linking a number of chromophores to a polymer chain backbone *via* a methyl ester group.[27] This was first demonstrated by our group using an amphiphilic diblock copolymer composed of hydrophilic PEO and a hydrophobic block of poly(1-pyrenylmethyl methacrylate) (PPyMA).[28] As shown in Fig. 5, upon UV irradiation of PEO-*b*-PPyMA micelles in aqueous solution, the photosolvolysis of pyrenylmethyl esters takes place, which cleaves 1-pyrenemethanol from the polymer and converts the ester groups to carboxylic acid groups and thus the hydrophobic PPyMA to the hydrophilic poly(methacrylic acid) (PMAA). SEM images show that core-shell micelles (~15 nm in diameter), prepared using $PEO_{45}$-*b*-$PPyMA_{72}$, observable before UV irradiation are disappeared after 15 min UV irradiation (365 nm, total intensity ~2 W, micellar solution ~3.5 mL).

This design was further validated by the use of an amphiphilic BCP bearing another chromophore.[29] As shown in Fig. 6, the BCP is composed of PEO and a hydrophobic block of poly(2-nitrobenzylmethyl methacrylate) (PNBMA). In this case, the photolysis reaction of 2-nitrobenzyl groups results in the cleavage of 2-nitrosobenzaldehyde from the polymer, which transforms the hydrophobic PNBMA into the hydrophilic PMAA and triggers the micellar dissociation. Using micelles prepared with a sample of $PEO_{45}$-*b*-$PNBMA_{167}$, the release of a loaded hydrophobic dye, Nile Red (NR), upon photoinduced dissociation of micelles was investigated by monitoring the fluorescence emission of NR. When released from the hydrophobic micelle core to an aqueous medium, NR is known to display fluorescence quenching and a red-shift of the maximum



Fig. 6 (A) Chemical structure and the photoreaction of a 2-nitrobenzene-containing amphiphilic diblock copolymer. The photolysis of 2-nitrobenzyl groups, which can be activated by absorption of UV (single photon) or near infrared (NIR) (two-photon), results in the cleavage of photochromic groups and converts the hydrophobic block into hydrophilic poly(methacrylic acid) (PMAA). (B) Normalized fluorescence vs. irradiation time for a Nile Red-loaded micellar aqueous solution exposed to UV light (365 nm) of various intensities, showing increase in the release rate of Nile Red upon dissociation of micelles with increasing UV light intensity. Adapted with permission from ref. 29.

emission wavelength.[30] The example result in Fig. 6 shows the plots of normalized fluorescence intensity of NR as a function of irradiation time for micellar solutions exposed to UV light of different intensities (365 nm, 0.7 mL micellar solution). It can be seen that no release takes place without UV exposure, while the release becomes faster with increasing UV light intensity. This is understandable because high UV intensity speeds up the photolysis of 2-nitrobenzyl groups and thus the disruption of BCP micelles. This result shows the possibility of using light to control the release rate of encapsulated molecules by varying the intensity of light. Moreover, the 2-nitrobenzyl chromophore has a couple of interesting features. First, unlike pyrenylmethyl esters whose photosolvolysis requires the presence of a nucleophilic solvent, the photoreaction of 2-nitrobenzylmethyl esters is an intramolecular rearrangement process and can occur both in solution and in the solid state. Secondly, the photolysis reaction of 2-nitrobenzene can also be activated through two-photon absorption of near infrared (NIR) light. The disruption of BCP micelles by NIR (~700–1000 nm) is particularly attractive for biomedical applications, because NIR has a deeper penetration through water and tissues and is less detrimental to healthy cells than UV.[30–32] Using a femtosecond IR laser (Ti:sapphire), the release of NR in aqueous solution of $PEO_{45}$-*b*-$PNBMA_{167}$ micelles upon absorption of NIR light at 700 nm was observed, but it proceeded slowly due to the low efficiency of two-photon absorption of 2-nitrobenzene.[29] A solution to resolve this problem would be the use of chromophores having a large two-photon absorption cross section, such as some coumarin-based
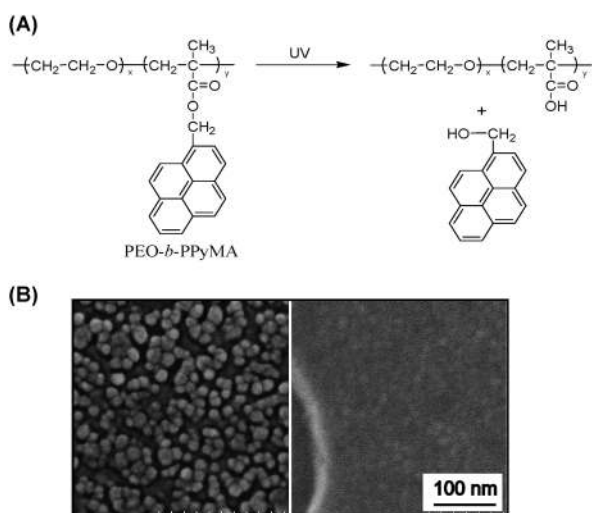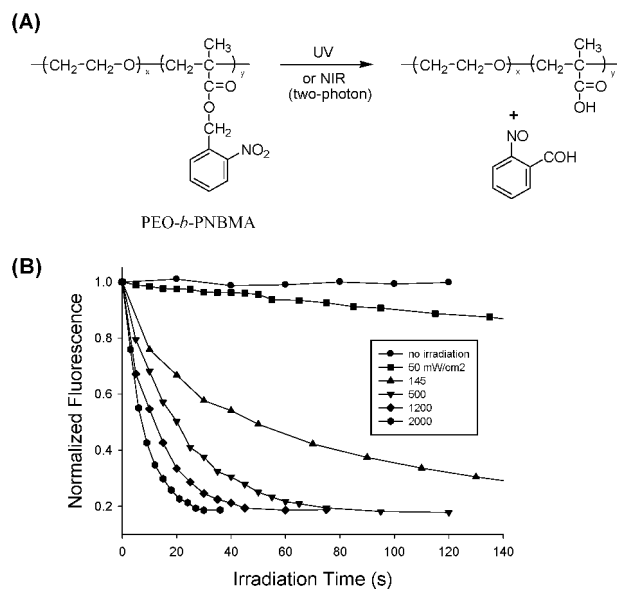


Fig. 5 (A) Chemical structure and the photoreaction of a pyrene-containing amphiphilic diblock copolymer. The UV light-induced photosolvolysis of pyrenylmethyl esters groups results in the cleavage of photochromic groups and converts the hydrophobic block into hydrophilic poly(methacrylic acid) (PMAA). (B) SEM images for a micellar solution cast on a silicon wafer: solution prior to UV irradiation (left) and the same solution after UV irradiation (365 nm) (right). Adapted with permission from ref. 28.

compounds.[31,32] Development of BCP micelles more sensitive to two-photon absorption of NIR is in progress in our laboratory.

An interesting development in using the photolysis reaction of 2-nitrobenzylmethyl esters to dissociate BCP micelles was reported by Jiang *et al.*[33] They made use of the photocleavage reaction in designing an amphiphilic BCP that is both photo- and thermosensitive, being composed of a hydrophilic block of PEO and a hydrophobic block that is a random copolymer of ethoxytri(ethylene glycol) acrylate and 2-nitrobenzyl acrylate. Micelles of this BCP are formed at temperatures above the lower critical solution temperature (LCST) of the thermosensitive block as it becomes insoluble in water. UV irradiation of the micellar solution, placed at a temperature close to the LCST, results in removal of 2-nitrobenzyl groups from the polymer and introduces the polar acrylic acid groups into the thermosensitive block. This structural change shifts the LCST to a higher temperature, so that BCP micelles are dissociated because the random copolymer block is below the new LCST. This study shows the potential of using the photocontrollable polarity to change the thermosensitivity of BCP micelles.

For controlled drug delivery, it may be advantageous to use a chromophore on the hydrophobic block, the photoreaction of which leads to the micellar dissociation without cleavage of the chromophore from the polymer, because the released compound may be a concern in terms of toxicity. We are not aware of such a report on BCPs until now, while some nice examples are known for micelles or vesicles of surfactant-like amphiphiles and amphiphilic random copolymers. Goodwin *et al.* used the Wolf rearrangement reaction of 2-diazo-1,2-naphthoquinones (DNQ), which can be activated by one-photon UV or two-photon NIR absorption, to photocontrol the dissociation of micelles formed by an amphiphile built up with a short poly(ethylene glycol) (PEG) chain and a hydrocarbon tail bearing a DNQ group on the end.[30] They showed that upon two-photon absorption of NIR, NR loaded in the micelles could be released into aqueous solution as a result of the Wolf rearrangement that converts the hydrophobic DNQ to the hydrophilic 3-indenecarboxylate. Tang *et al.* partially functionalized hydrophilic poly(hydroxyethyl methacrylate) with hydrophobic DNQ pendant groups and found that vesicles formed by this random copolymer could be disintegrated to smaller spherical particles upon UV light-induced Wolf rearrangement.[34] In another report, Jiang *et al.* synthesized PEG terminated with a hydrophobic triphenyl-methane dye.[35] This amphiphile could form vesicles with the dye molecules constituting the membrane; upon UV irradiation, triphenylmethane groups are converted to the charged form, leading to the disassembly of the vesicles. In those cases, no chromophore cleavage is involved. In principle, those chromophores can be used to design BCPs for irreversibly photo-dissociable micelles. While recognizing the interest of exploring photoreactions other than photoinduced cleavage to trigger an irreversible dissociation of BCP micelles, it is also possible to take advantage of the cleavage reaction. Knowing that many drugs or bioagents are compounds containing aromatic rings, it would be possible to make them photo-cleavable pendant groups on the hydrophobic block like PPyMA and PNBMA as discussed above.[28,29] In such a case, the photocleavage and release of the carried drug parallels the micellar dissociation and can really be made to happen at a chosen time and location. Of course,

a greater synthetic effort is required to covalently attach the drug to the hydrophobic block through a methyl ester group.

## 4. Reversible cross-linking

Again, in the context of controlled drug delivery, following administration of polymer micelles in the body, some micellar systems may fall apart upon dilution to below their critical micelle concentrations (c.m.c.). And encapsulated molecules could also leak out quickly due to interactions of the micelles with the complex biological environment.[36] These are undesired events that need to be prevented from occurring, because they render any strategies for site-specific transportation of micelles and on-site release of loaded compounds useless. A well-known approach is to chemically cross-link polymer micelles, either micelle core[37,38] or micelle shell,[39,40] which ensures the structural integrity of micelles and could also slow the leakage of encapsulated molecules through diffusion across the polymer. However, stabilized polymer micelles may be problematic at a later time. After they reach the target, the stability may render the on-site release more difficult; a stimulus is still needed to disrupt the micelles and to facilitate the release. This is where another type of photocontrol using rationally designed photo-active BCPs comes in, namely, reversible cross-linking and de-cross-linkng using a reversible photoreaction. The strategy is schematically illustrated in Fig. 7, where the hydrophobic block bears photochromic groups that can undergo reversible cross-linking and de-cross-linking reactions upon absorption of light at two different wavelengths. With such a photoreaction, it is possible to use light to cross-link polymer micelles (both core and shell for normal and reverse micelles, respectively), which affords the required micellar stability, and subsequently to use light to de-cross-link the micelles for their destabilization.

We have demonstrated this concept by using the reversible photodimerization reaction of coumarin.[41] For micelles of BCPs containing coumarin pendant groups on the hydrophobic block, upon absorption of photons of $\lambda > 310$ nm, coumarin moieties can dimerize through a cycloaddition reaction, giving rise to micelle cross-linking; while upon absorption at $\lambda < 260$ nm, photoinduced cleavage of cyclobutane bridges can occur leading to micelle de-cross-linking. The designed amphiphilic BCP has the chemical structure shown in Fig. 8, with PEO as the hydrophilic block and a poly(coumarin methacrylate) (PCMA), or a random copolymer of CMA and methyl methacrylate (P(CMA-*co*-MMA)), as the hydrophobic block. Its micelles in
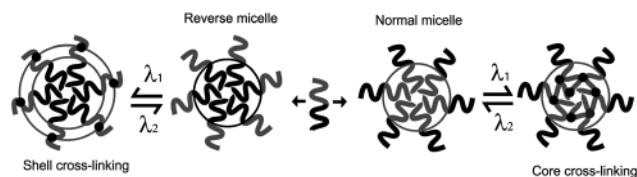


**Fig. 7** Schematic illustration of block copolymer micelles that can be reversibly cross-linked and de-cross-linked by light at two different wavelengths. The process is controlled by a reversible photodimerization and photocleavage reaction of photochromic groups. Both micelle core cross-linking and shell cross-linking can be realized for normal (hydrophobic core) and reverse micelles (hydrophilic core) respectively.

This journal is © The Royal Society of Chemistry 2009

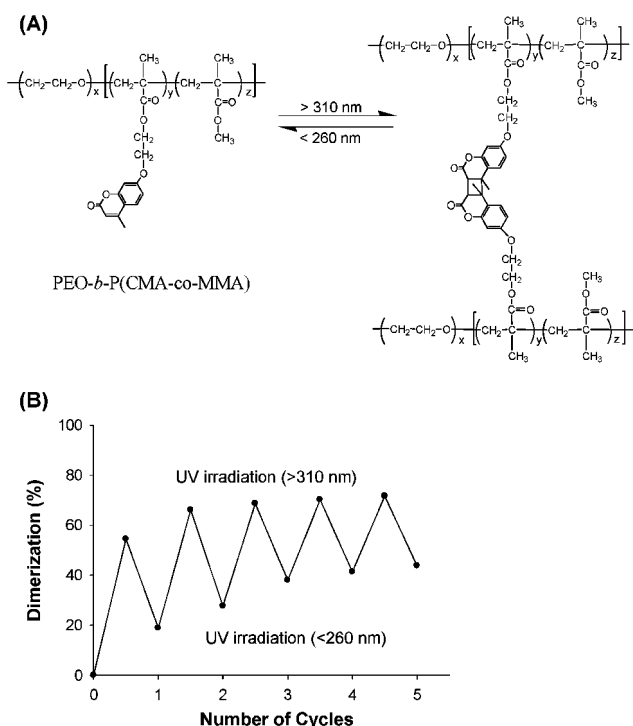*J. Mater. Chem.*, 2009, **19**, 4887–4895 | **4891**

Fig. 8 (A) Chemical structure and the photoreaction of a coumarin-containing amphiphilic diblock copolymer, whose micelle core can be reversibly cross-linked and de-cross-linked by the photodimerization of coumarin groups and the photocleavage of cyclobutane bridges at different wavelengths. (B) Changes in the photodimerization degree with a micellar aqueous solution subjected to alternating UV irradiation at $\lambda >$ 310 nm and $\lambda <$ 260 nm. Adapted with permission from ref. 41.

aqueous solution indeed can undergo reversible core cross-linking and de-cross-linking upon exposure to UV light at different wavelengths. The example result in Fig. 8 was obtained with an aqueous micellar solution of $PEO_{112}$-$b$-$P(CMA_8$-$co$-$MMA_{20})$ (2 mL). It shows the reversible variation of the dimerization degree (estimated from the change in absorption of coumarin groups) upon a number of cycles of alternating UV irradiations at $\lambda >$ 310 nm (2 W) and $\lambda_{max} =$ 254 nm (1.25 W). The de-cross-linking reaction (cleavage of cyclobutane ring) appears to be less efficient than the cross-linking reaction (coumarin dimerization), suggesting a photostationary state with equilibrated populations of the two isomeric forms of the chromophore. The photo-cleavage reaction could be more efficient by using a light source that minimizes the dimerization reaction occurring at the same time. The effect of micelle core cross-linking and de-cross-linking on the release rate of entrapped NR into a THF/water (2/3, v/v) solution was investigated by monitoring NR's fluorescence emission.[41] The results revealed that micelle core cross-linking could slow the release rate while subsequent micelle core de-cross-linking could recover the release rate partly, showing the potential of this photocontrol concept: using light to afford both the stabilization of encapsulation and the destabilization of micelles for controlled release at the required time and location.

In organic solvents, BCPs can form reverse micelles with a core of the hydrophilic block and a shell of the hydrophobic block. The micelle shell can thus be cross-linked and de-cross-linked

using light if the hydrophobic block bears coumarin pendant groups. The preparation of such shell-cross-linked revere micelles (SCRM) and its use for the preparation of stimuli-responsive polymer nanoparticles were demonstrated using an amphiphilic BCP whose hydrophilic block is poly(dimethylaminoethyl methacrylate) (PDMAEMA) and whose hydrophobic block is a random copolymer of coumarin methacrylate and methyl methacrylate (P(CMA-$co$-MMA)) (Fig. 9).[42] Using a sample of $PDMAEMA_{54}$-$b$-$P(CMA_{19}$-$co$-$PMMA_{55})$, reverse micelles were obtained by quaternization of the tertiary amine groups of PDMAEMA upon addition of hydrochloric acid (HCl), which renders the PDMAEMA block insoluble in a mixed organic solvent of $THF/CH_2Cl_2$ (1/1, v/v) and leads to the formation of reverse micelles. Fig. 9 shows the result of size exclusion chromatograph (SEC) measurements that confirmed the excellent micelle stabilization after shell cross-linking with UV light at $\lambda >$ 310 nm and the subsequent destabilization of SCRM upon photo-de-cross-linking with UV light at $\lambda <$ 260 nm. Indeed, for non-cross-linked reverse micelles, the addition of some triethylamine in the solution, which traps HCl and converts
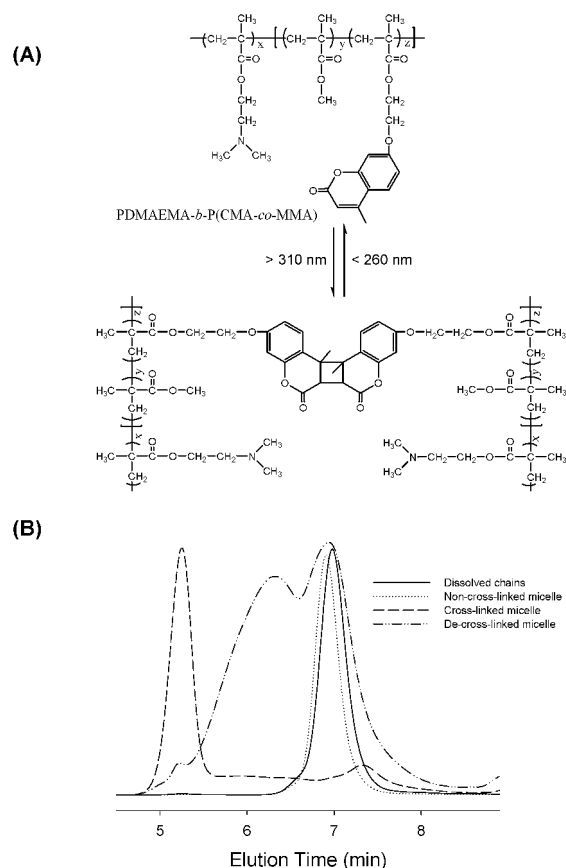


Fig. 9 (A) Chemical structure and the photoreaction of a coumarin-containing amphiphilic diblock copolymer used for the preparation of shell-cross-linked reverse micelles (SCRM). (B) Size exclusion chromatography (SEC) traces of reverse micelle solutions with and without shell cross-linking upon UV irradiation at $\lambda >$ 310 nm. While non-cross-linked reverse micelles are dissociated in the presence of triethylamine displaying almost the same elution time as molecularly dissolved polymer, SCRM remain intact. But SCRM are disintegrated after shell-de-cross-linking upon UV irradiation at $\lambda <$ 260 nm. Adapted with permission from ref. 42.

the PDMAEMA block back to the non-quaternized form, led to their total dissolution, displaying a peak at almost the same place as molecularly dissolved BCP. By contrast, shell-cross-linked micelles were completely stable in the presence of triethylamine, showing a peak at lower elution time corresponding to the preserved micellar aggregates. After the SCRM solution was subjected to the photo-de-cross-linking, they were disintegrated showing a peak at longer elution time corresponding to dissolved chains and a broad peak at intermediate elution times arising from disrupted micellar aggregates (only a very small fraction of SCRM remains unaffected). In the same work, it was further demonstrated that the use of such structurally locked SCRM made it possible to carry out micelle surface initiated atom transfer radical polymerization (ATRP) to graft an outer corona on SCRM. The "decoration" with PDMAEMA gives rise to water soluble polymer nanoparticles that are sensitive to light, pH and temperature changes.[42] Although UV light was used so far in the reported studies, the reversible photo-cross-linking would be possible using visible light through two-photon absorption with some coumarin derivatives.[43,44]

The control over polymer micelles using a reversible photo-cross-linking reaction offers many possibilities in designing new systems. For instance, it is easy to imagine an ABC-type triblock copolymer with hydrophilic A, hydrophobic C and a coumarin-containing B block that can either be hydrophilic or hydrophobic. In both cases, if the BCP forms core-shell-corona micelles, the shell can be photo-cross-linked to separate the core from the corona and to regulate the diffusion of guest molecules between the inner and outer areas. The particular interest here is the possibility to reversibly change the cross-linking degree of the shell to adjust the rate of diffusing. Of course, other photochromic molecules capable of reversible cross-linking and de-cross-linking photoreactions, such as anthracene[45] and cinnamic moieties,[46] can be explored in the same way as with coumarin.

## 5. Morphological transition

The photoinduced dissociation of polymer micelles in solution is not an instantaneous process; it should be viewed as a disruption process that continuously evolves in time upon illumination. The kinetics largely depends upon the rate of the responsible photoreaction that, in turn, is determined not only by how fast and how efficient the photoreaction itself proceeds, but also very much by the used experimental conditions (polymer concentration, solution volume and light intensity). For example, the BCP concentration in the micellar solution can be crucial. Generally, the photoreaction is not complete; it basically increases the polarity of the hydrophobic block. When this happens, the resulting shift of the hydrophilic-hydrophobic balance could only be an increase of the critical micelle concentration (c.m.c.) of the BCP. If the micelles are prepared with a polymer concentration far above the initial c.m.c., the photoinduced shift may not be important enough to bring the BCP to below the new c.m.c. and no micellar dissociation would be observed. However, even without dissociation, significant changes in the micellar aggregation state could take place as a result of the photoreaction. If the polarity of the micelle core increases, it may become more hydrated (or solvated) and result in a swelling of the

micelle. There are also several reports on photoinduced deformation and fusion of micelles or vesicles prepared using azobenzene-containing BCPs.[47–49] It should be emphasized that the release of loaded guest molecules does not require complete dissociation of micelles.

Without dissociation, the change in the micellar aggregation state, corresponding to a morphological transition, can be optically controlled to some extent. Han *et al.* synthesized a diblock copolymer composed of poly(*N*-isopropylacrylamide) (PNIPAm) and poly{6-[4-(4-pyridylazo)phenoxy]hexylmethacrylate} (PNIPAm-*b*-PAzPy).[50] They reported that in a mixed solvent of water/tetrahydrofuran, the sample of PNIPAm$_{135}$-*b*-PAzPy$_{54}$ could form giant, micrometer-sized vesicles with the PAzPy block in the membrane, observable directly on an optical microscope. Upon UV irradiation, the trans-cis isomerization of azopyridine groups gave rise to an increase in size of the vesicles by as much as 17%, while the initial size was recovered upon subsequent visible irradiation. A change in packing of azopyridine groups or solubility of the PAzPy block in the solvent could account for the reversible swelling and contraction of the vesicles.

Another nice example of photocontrolled morphological transition was reported by Liu and Jiang who designed a "graft-like" copolymer by linking a carboxy group-terminated polybutadiene (CPB) to an azobenzene-containing random copolymer, poly(4-phenylazo-maleinanil-co-4-vinylpyridine) (AzoMI-VPy), through H-bonding between the carboxyl and pyridyl groups.[51] As schematized in Fig. 10, with azobenzene moieties in the trans form, this interpolymer complex is soluble in toluene. Under UV light irradiation, the increase in polarity with azobenzene in the cis form renders AzoMI-VPy insoluble, leading to the formation of micelles with AzoMI-VPy in the core and CPB forming the corona remained soluble in the solvent. Micelles are dissociated upon visible light irradiation that brings azobenzene back to the trans form. More interestingly, if the AzoMI-VPy micelle core is chemically cross-linked to afford the structural integrity (reaction between pyridyl groups and 1,4-diiodobutene at room temperature in the dark), subsequent visible light irradiation can no longer dissociate the micelles due
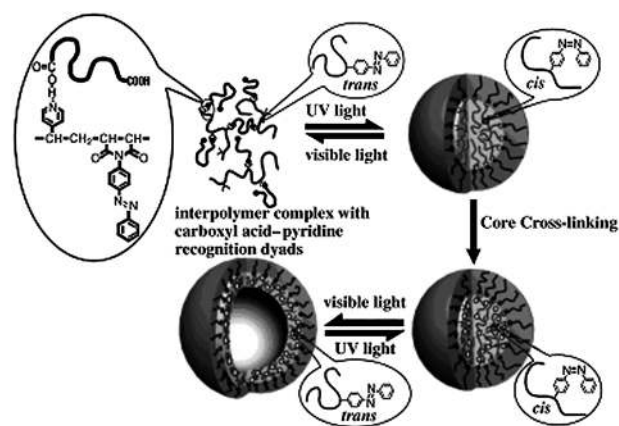


**Fig. 10** Schematic illustration of the photoinduced reversible micellization and micelle-to-hollow sphere transition in toluene for an azobenzene-containing random copolymer hydrogen-bonded to polybutadiene. Reproduced with permission from ref. 51.

This journal is © The Royal Society of Chemistry 2009

*J. Mater. Chem.*, 2009, **19**, 4887–4895 | 4893

to the cross-linking. But the solubility of AzoMI-VPy with trans azobenzene allows the core to absorb the solvent, which transforms the core-shell micelles (~250 nm) into larger hollow spheres (~900 nm). Upon UV irradiation, core-shell micelles can be recovered, and this morphological transition is reversible.

The basic mechanism of such a photoinduced morphological transition is the same as that for photoinduced dissociation of BCP micelles, that is, a photocontrolled change in polarity or solubility of the hydrophobic block. In case the photoreaction turns the hydrophobic block into a water-soluble block, the additional requirement is the cross-linking that prevents the micelles from total dissolution. This approach can be adapted to many BCPs. For example, with the PEO-b-PPyMA or PEO-b-PNBMA micelles in aqueous solution (Fig. 5 and 6), if the hydrophobic micelle core is slightly cross-linked, the photoinduced transformation of PPyMA or PNBMA to PMAA should only result in a swelling of the micelles; the degree of swelling should be controlled by the cross-linking degree. It can also be expected that if the two blocks of PEO and PPyMA, or PEO and PNBMA, are linked by a cross-linkable middle block (bearing coumarin groups, for example), a shell cross-linking would prevent the dissociation of those ABC-type BCP micelles and allow them to swell. In case the photoreaction only increases the c.m.c., micelle cross-linking may not be necessary if the BCP concentration is above the new c.m.c. Without cross-linking, in addition to swelling, morphological transitions between different micellar aggregates (for example, from core-shell micelle to vesicle) could be observed. Of course, depending on the reversibility of the used photoreaction, the photoinduced morphological transition may be reversible or irreversible.

## 6. Outlook

The recent achievement in the field of photocontrollable BCP micelles opens the door to more exciting developments. The interest of the revealed design principles and underlying mechanisms may go beyond BCP micelles. They can be exploited for other self-assembled amphiphilic polymers or materials systems, for which optically enabled temporal and positional control of properties, functions or morphology is desired. To make light a truly appealing and viable stimulus for controlled BCP micelle-based drug delivery, much works remain to be done. The transfer of knowledge to designing photocontrollable, biocompatible and biodegradable BCP micelles is obviously necessary. It is also of fundamental importance to achieve a better understanding of the photoinduced processes on the molecular level. This is quite challenging because the interrelated events (photoreaction of the chromophore, disruption of micelles and release of guest molecules) should be investigated simultaneously.[52] Discussed below are some other challenging issues that need to be addressed and that represent exciting opportunities.

First, one would like to have *more precise control* over BCP micelles by using light. One example is the photoinduced dissociation with a desired or programmable rate. As mentioned earlier, unless the photoreaction turns the hydrophobic block into a water soluble one, the increased polarity should shift the c.m.c. to a higher concentration; the dissociation of micelles occurs if the BCP concentration is below the new c.m.c. Systematic investigations are required to understand, among other things, 1) how the c.m.c. is shifted as a function of the polarity change that, in turn, is determined by the photoreaction degree with a given chromophore; 2) what is the effect of the absolute and relative block lengths on the photoinduced shift of c.m.c. and on the rate of micellar dissociation; and 3) how the BCP concentration is related to the dissociation rate. Knowledge gained from these fundamental studies can also help us to understand the conditions under which photoinduced dissociation can be achieved with the use of a small amount of photochromic groups. Such an amplification effect is important since the used chromophore may be a concern for toxicity.

Second, BCP micelles dissociable upon exposure to NIR light through one-photon absorption is an example of *more difficult control*. As mentioned previously, the use of NIR light is more attractive for biological applications. It is possible that the sensitivity of BCP micelles to two-photon absorption of NIR could be improved in the near future through the use of chromophores having a large two-photon absorption cross section. However, the required femtosecond IR laser with high-energy pulses for two-photon absorption can limit the interest for practical uses. If BCP micelles can be disrupted by continuous-wave NIR from a diode laser, the cheaper and more-accessible NIR light source would make the concept of light-controlled drug delivery more appealing. The challenge here is to develop chromophores that, upon single-photon absorption of NIR, can display a structural or conformational change leading to an increased polarity. An alternative BCP design strategy is to make a hydrophobic block that is a random copolymer bearing both NIR-sensitive dye and thermally labile groups, with the used dye being an efficient heat generator upon one-photon absorption of NIR light. The idea is to use the photo-generated heat inside the micelle core to trigger a cleavage reaction of the thermo-sensitive groups, the consequence of which is a structural change that increases the polymer polarity. The challenge is to know how to generate a sufficient amount of heat for the thermal cleavage despite the fast dissipation of heat in the micellar solution.

Third, knowing how to achieve *more complex control* of BCP micelles by light is another research direction worth effort. On one hand, a combined use of photoinduced change in polarity and photocontrolled cross-linking may be an interesting route to explore. For example, one can synthesize an amphiphilic BCP composed of PEO and a hydrophobic block that bears both photo-cross-linkable coumarin and photocleavable 2-nitrobenzene pendant groups. It is conceivable that UV irradiation of its vesicles in aqueous solution could initiate simultaneously the photo-cross-linking and photocleavage reactions. This may produce polymer vesicles with a cross-linked yet hydrophilic membrane, whose porosity can be controlled through the reversible photo-cross-linking that allows one to adjust the diffusion of molecules through the membrane. On the other hand, combining the use of light with a different stimulus such as pH or temperature change offers new possibilities to design BCP micelles with a more complex level of control. For instance, the photocleavage reaction can be used to introduce carboxylic acid groups on a random copolymer block, which not only may shift the LCST for a thermosensitive polymer,[33] but could also affect the pH sensitivity if the polymer is a weak polyacid or polybase.

## Acknowledgements

## References

1 V. P. Torchilin, *Adv. Drug Deliv. Rev.*, 1995, **47**, 295.
2 D. E. Discher and A. Eisenberg, *Science*, 2002, **297**, 967.
3 R. Haag, *Angew. Chem. Int. Ed.*, 2004, **43**, 278.
4 G. Gaucher, M. H. Dufresne, V. P. Sant, N. Kang, D. Maysinger and J. C. Leroux, *J. Control. Release*, 2005, **109**, 169.
5 C. F. van Nostrum, *Adv. Drug Deliv. Rev.*, 2004, **56**, 295.
6 E. R. Gillies and J. M. J. Frechet, *Chem. Commun.*, 2003, 1640.
7 E. G. Bellomo, M. D. Wyrsta, L. Pakstis, D. J. Pochan and T. J. Deming, *Nat. Mater.*, 2004, **3**, 244.
8 Y. Bae, S. Fukushima, A. Harada and K. Kataoka, *Angew. Chem. Int. Ed.*, 2003, **42**, 4640.
9 J. Du, Y. Tang, A. L. Lewis and S. P. Armes, *J. Am. Chem Soc.*, 2005, **127**, 17982.
10 J. E. Chung, M. Yokoyama and T. Okano, *J. Control. Release*, 2000, **65**, 93.
11 C. M. Schilli, M. Zhang, E. Rizzardo, S. H. Thang, Y. K. Chong, K. Edwards, G. Karlsson and A. H. E. Muller, *Macromolecules*, 2004, **37**, 7861.
12 S. Qin, Y. Geng, D. E. Discher and S. Yang, *Adv. Mater.*, 2006, **18**, 2905.
13 E. R. Gillies and J. M. J. Fréchet, *Pure Appl. Chem.*, 2004, **76**, 1295.
14 J. Rodriguez-Hernandez, F. Checot, Y. Gnanou and S. Lecommandoux, *Prog. Polym. Sci.*, 2005, **30**, 712.
15 C. J. F. Rijchen, O. Soga, W. E. Hennink and C. F. van Nostrum, *J. Control. Release*, 2007, **120**, 131.
16 J. Y. Shin and N. L. Abbott, *Langmuir*, 1999, **15**, 4404.
17 Y. Einaga, O. Sato, T. Iyoda, A. Fujishima and K. Hashimoto, *J. Am. Chem. Soc.*, 1999, **121**, 3745.
18 C. T. Lee, K. A. Smith and T. A. Hatton, *Macromolecules*, 2004, **37**, 5397.
19 J. Eastoe and A. Vesperinas, *Soft Matter*, 2005, **1**, 338.
20 Y. Wang, N. Ma, Z. Wang and X. Zhang, *Angew. Chem. Int. Ed.*, 2007, **46**, 2823.
21 G. Wang, X. Tong and Y. Zhao, *Macromolecules*, 2004, **37**, 8911.
22 G. Mayer and A. Heckel, *Angew. Chem. Int. Ed.*, 2006, **45**, 4900.
23 X. Tong, G. Wang, A. Soldera and Y. Zhao, *J. Phys, Chem. B*, 2005, **109**, 20281.
24 H. Lee, W. Wu, J. K. Oh, L. Mueller, G. Sherwood, L. Peteanu, T. Kowalewski and K. Matyjaszewski, *Angew. Chem. Int. Ed.*, 2007, **46**, 2453.
25 A. Natansohn and P. Rochon, *Chem. Rev.*, 2002, **102**, 4139.
26 T. Ikeda, *J. Mater. Chem.*, 2003, **13**, 2037.
27 J. Pincock, *Acc. Chem. Res.*, 1997, **30**, 43.
28 J. Jiang, X. Tong and Y. Zhao, *J. Am. Chem. Soc.*, 2005, **127**, 8290.
29 J. Jiang, X. Tong, D. Morris and Y. Zhao, *Macromolecules*, 2006, **39**, 4633.
30 A. P. Goodwin, J. L. Mynar, Y. Ma, G. R. Fleming and J. M. J. Fréchet, *J. Am. Chem. Soc.*, 2005, **127**, 9952.
31 T. Furuta, S. S.-H. Wang, J. L. D. Dantzker, T. M. Dore, W. J. Bybee, E. M. Callaway, W. Denk and R. Y. Tsien, *Proc. Natl. Acad. Sci. USA*, 1999, **96**, 1193.
32 Y.-R. Zhao, Q. Zheng, K. Dakin, K. Xu, M. L. Martinez and W.-H. Li, *J. Am. Chem. Soc.*, 2004, **126**, 4653.
33 X. Jiang, C. A. Lavender, J. W. Woodcock and B. Zhao, *Macromolecules*, 2008, **41**, 2632.
34 F. Tang, Y. Yu, C. Wang and S. Yang, *Macromolecules*, 2008, **41**, 3385.
35 Y. Jiang, Y. Wang, N. Ma, Z. Wang, M. Smet and X. Zhang, *Langmuir*, 2007, **23**, 4029.
36 N. Kang, M.-E. Perron, R. E. Prud'homme, Y. Zhang, G. Gaucher and J.-C. Leroux, *Nano Lett.*, 2005, **5**, 315.
37 A. Guo, G. Liu and J. Tao, *Macromolecules*, 1996, **29**, 2487.
38 T. K. Bronich, P. A. Keifer, L. S. Shlyakhtenko and A. V. Kabanov, *J. Am. Chem. Soc.*, 2005, **127**, 8236.
39 K. B. Thurmond, T. Kowalewski and K. L. Wooley, *J. Am. Chem. Soc.*, 1996, **118**, 7239.
40 S. Lui and S. P. Armes, *J. Am. Chem. Soc.*, 2001, **123**, 9910.
41 J. Jiang, B. Qi, M. Lepage and Y. Zhao, *Macromolecules*, 2007, **40**, 790.
42 J. Babin, M. lepage and Y. Zhao, *Macromolecules*, 2008, **41**, 1246.
43 S. R. Trenor, A. R. Shultz, B. J. Love and T. E. Long, *Chem. Rev.*, 2004, **104**, 3059.
44 K. D. Belfield, M. V. Bondar, Y. Liu and O. V. Przhonska, *J. Phys. Org. Chem.*, 2003, **16**, 69.
45 X.-A. Trinh, J. Fukuda, Y. Adachi, H. Nakanishi, T. Norisuye and Q. Tran-Cong-Miyata, *Macromolecules*, 2007, **40**, 5566.
46 A. Lendlein, H. Jiang, O. Junger and R. Langer, *Science*, 2005, **434**, 879.
47 W. Su, Y. Luo, Q. yan, S. Wu, K. Han, Q. Zhang, Y. Gu and Y. Li, *Macromol. Rapid Commun.*, 2007, **28**, 1251.
48 D. Wang, G. Ye and X. Wang, *Macromol. Rapid Commun.*, 2007, **28**, 2237.
49 S. L. Sin, L. H. Gan, X. Hu, K. C. Tam and Y. Y. Gan, *Macromolecules*, 2005, **38**, 3943.
50 K. Han, W. Su, M. Zhong, Q. Yan, Y. Luo, Q. Zhang and Y. Li, *Macromol. Rapid Commun.*, DOI: 10.1002/marc.200800483.
51 X. Liu and M. Jiang, *Angew. Chem. Int. Ed.*, 2006, **45**, 3846.
52 Y. Zhao, *Chem. Rec.*, 2007, **7**, 286.

This journal is © The Royal Society of Chemistry 2009

*J. Mater. Chem.*, 2009, **19**, 4887–4895 | 4895