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For Table of Contents Entry

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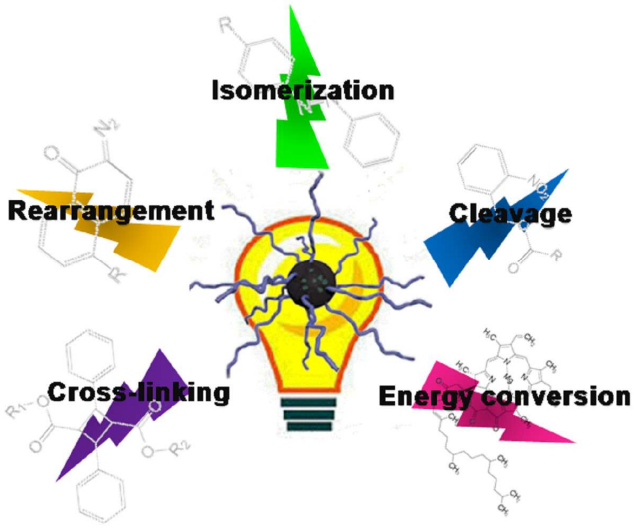

The photo-responsive polymeric micelles with different photo-reaction mechanisms and their applications in various of fields have been discussed.

Photo-responsive polymeric micelles

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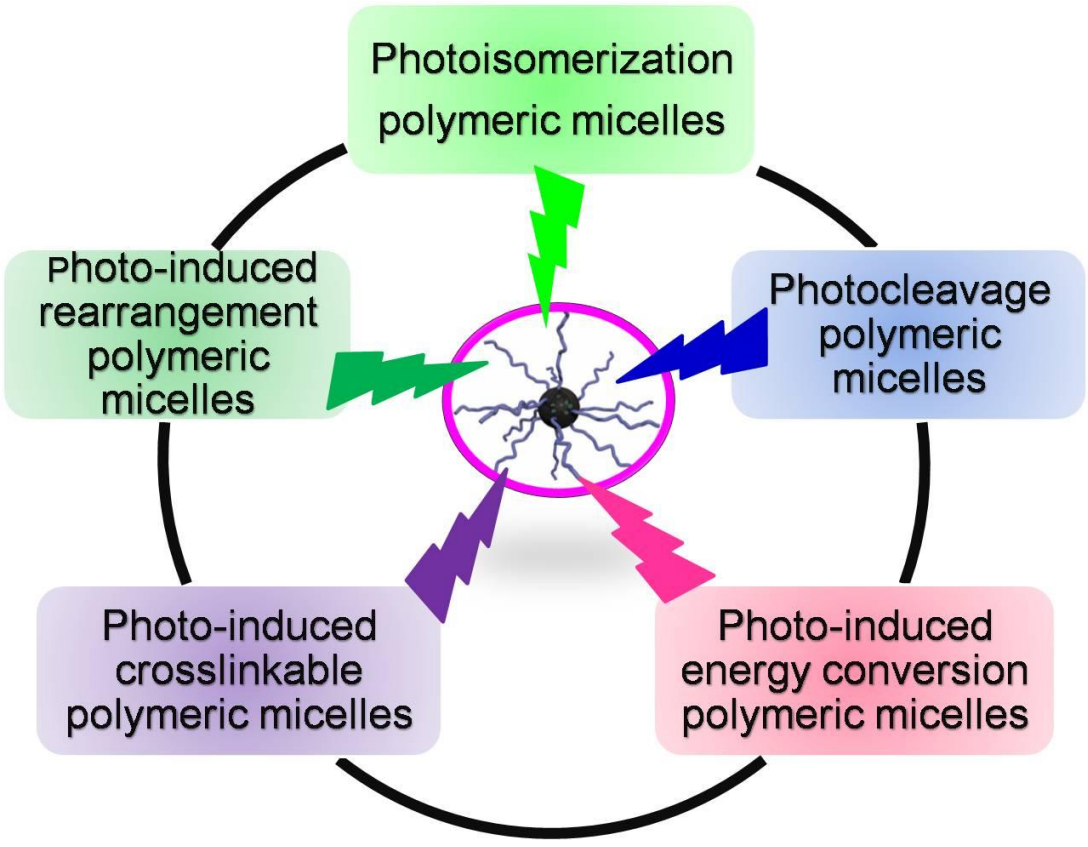
Abstract: Photo-responsive polymeric micelles have received increasing attention in both academic and industrial fields due to their efficient photo-sensitive nature and unique nanostructure. In view of photo-reaction mechanism, the photo-responsive polymeric micelles can be divided into five major types: (1) photoisomerization polymeric micelles, (2) photo-induced rearrangement polymeric micelles, (3) photocleavage polymeric micelles, (4) photo-induced crosslinkable polymeric micelles, and (5) photo-induced energy conversion polymeric micelles. This review highlights the recent advances of photo-responsive polymeric micelles, including the design, synthesis and applications in various biomedical fields. Especially, the influence of different photo-reaction mechanisms on the morphology, structure and properties of the polymeric micelles is emphasized. Finally, the possible future directions and perspectives in this emerging area are briefly discussed.

1. Introduction

As one important smart material, responsive polymers are capable of adapting to various internal or external stimuli, such as enzyme,[1-3] sugar,[4-7] pH,[8-16] redox,[17-22] ultrasound,[23,24] temperature,[25-34] and light,[35-46] Among these available stimuli, light is a particularly interesting option. It is a clean and highly efficient stimulation source. Different from other stimuli, light can be triggered from outside of the system and controlled both spatially and temporally with great ease and convenience. Indeed, photo-reaction processes can start/stop when the light is switched on/off, which does not require any additional reagents. Moreover, the wavelength and intensity of light can be readily adjusted during the reaction process to intelligently control the properties of polymers. Recently, light-responsive polymers have attracted more and more interest. One of the main sources for the development in the broad area of light-responsive polymers is their potential applications in the biomedical fields. In fact, there are several elegant reviews in this area.[47-54] Here, we only focus our interest on the recent advances in the development of photo-responsive polymeric micelles and their applications in biomedical fields.

A wide variety of polymeric systems are related with light, including photodynamic therapy system (PDT),[55,56] fluorescence resonance energy transfer (FRET),[57-60] photo-induced complexation,[61-63] and so on. Here, only light-responsive polymeric micelles are discussed. Before discussing the light-responsive polymeric micelles, a brief classification for light-responsive polymeric micelles might be helpful. We have noted that Zhao and coworkers classified photo-responsive polymeric micelles into several different categories according to the photo-induced structural changes and the reversible characteristics.[48,51,52] In our review, considering the difference of photo-reaction mechanisms and the effect of light on each photo-responsive group, we regroup the photo-responsive polymeric micelles into five types (**Scheme 1**): (1) photoisomerization polymeric micelles, (2) photo-induced rearrangement polymeric micelles, (3) photocleavage polymeric micelles, (4) photo-induced crosslinkable polymeric micelles, and (5) photo-induced energy conversion polymeric micelles. Apparently, photo-responsive polymeric micelles are a diverse research area, not only in the types of the photo-responsive groups, but also in the fascinating features of the photo-responsive polymeric micelles. In the following sections, we firstly summarize varied photo-responsive groups and the unique features of the resulting photo-responsive polymeric micelles, followed by the recent developments of each type of photo-responsive polymeric micelles as remarkable examples.



Scheme 1 Five different photo-responsive polymeric micelles

2. Photo-responsive groups

Photo-responsive polymeric micelles are typically constructed *via* the self-assembly of an amphiphilic block copolymer with a functional photochromic chromophore (**Table 1**). The optical signal is firstly captured by the photochromic molecules.[47-49,64] Next, the chromophores in the photoreceptor convert the photo-irradiation to a chemical signal through a photoreaction such as isomerization, rearrangement, cleavage, dimerization and energy conversion. The chemical signal is transferred to the functional part of micelles, resulting in the control of their properties. The change of the chromophores upon photo-irradiation strongly depends on their molecular structures and variable light sources.

Table 1 Typical examples of photo-responsive groups and correspondent features of photo-responsive polymeric micelles

Photo-responsive group	Reaction	Irradiation	Reversibility	Reference
Photoisomerization				
Azobenzene	*Trans* to *cis*	UV	Yes	37,39,41-44, 48,51-53, 65-69,124-137
	Cis to *trans*	Visible light	Yes	
Spiropyran	Closed to open	UV	Yes	3,48,51-53,65, 71,73-75,149
	Open to closed	Visible light	Yes	
Dithienylethene	Closed to open	UV	Yes	48,51-53,72, 76-78
	Open to closed	Visible light	Yes	
Photo-induced rearrangement				
2-Diazo-1,2-naphthoquinone	Wolff rearrangement	UV or NIR	No	48,51-53,79-82,83-92
Photocleavage				
o-Nitrobenzyl ester	Cleavage	UV or NIR	No	40,45,48,51-53,104-107,150
Coumarinyl ester	Cleavage	UV or NIR	No	48,51-53,105, 107
Pyrenylmethyl ester	Cleavage	UV	No	40,48,51-53
Photo-induced crosslinking				
Cinnamic acid	Dimerization	UV	Yes	112-114
Cinnamic ester	Dimerization	UV	No	48,51-53, 109-111,115
Coumarin	Dimerization	UV	Yes	48,51-53, 116-119

3. Photoisomerization polymeric micelles

Photoisomerization is a molecular behavior in which structural change between isomers is caused by photo-excitation. This process is often reversible and repeatable, making these photoisomerization groups attractive candidates in diverse forms to functionalize polymers in broad range of applications. Several typical photoisomerization molecules have been used for designing polymeric micelles, including azobenzene (AZO), spiropyran (SP), and dithienylethene (DTE).

3.1 AZO-containing photoisomerization micelles

The conformation of AZO and its derivatives changes from the apolar *trans* form to the polar *cis* form upon light irradiation (340-380 nm), but this process reforms back when undergoing a subsequent irradiation at 420-490 nm or moving into the dark.[51,65-67] The *trans*-AZO form (dipole moment, μ = 0D) is less polar and more hydrophobic than the *cis*-AZO form (μ = 3D), which may induce the assembly and disruption of AZO-containing polymeric micelles in a reversible manner. Based on this phenomenon, Zhao and coworkers have constructed a photoisomerization polymeric micelle system that is disrupted upon ultraviolet (UV) light irradiation and reforms itself when irradiated with visible light.[48,68,69] This system is based on an amphiphilic diblock copolymer composed of a hydrophilic block of poly(*t*-butyl acrylate-*co*-acrylic acid) and a hydrophobic block of poly(methacrylate) bearing AZOs as the side-chain groups (**Fig. 1**). Spherical micelles can be observed from the self-assembly of this amphiphilic copolymer in a dioxane-water mixture. Under UV light irradiation, the side-chain AZO groups are isomerized from the apolar *trans* form to the polar *cis* form, resulting in the disruption of the micellar aggregates. However, when visible light is applied, AZO groups convert back to the *trans* form and the polymeric micelles reproduce. Clearly, upon the alternating irradiation with UV and visible light, the micelle disruption and formation can be reversibly induced by adjusting the hydrophilicity-hydrophobicity balance in AZO-containing copolymers.

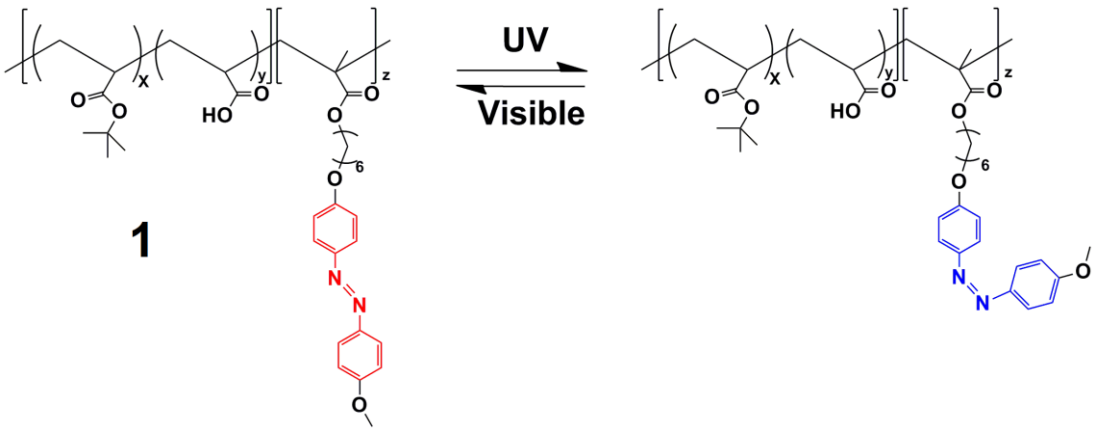


Fig. 1 Representative amphiphilic copolymers **1** bearing AZO groups used for the reversible light-induced disruption and formation of aqueous micelles. Reproduced from ref. 68. Copyright 2004 American Chemical Society.

Jiang and coworkers developed the "block-copolymer-free" strategy to construct polymeric micelles and hollow spheres by interpolymer-specific interactions.[70] They used homopolymers, random copolymers, and oligomers as building blocks to construct non-covalently connected micelles (NCCMs), in which core and shell were connected by intermolecular interactions. For example, they reported a photo-controllable self-assembled system comprising of poly(4-phenylazomaleinanil-*co*-4-vinylpyridine) (AZOMI-VPy) and polybutadiene with a terminal carboxy group (CPB). First, the AZOMI-VPy/CPB formed "graft-like" interpolymer complexes in toluene owing to the hydrogen bonding interaction between carboxylic acid and pyridine. The complexes were soluble in toluene when the AZO units of AZOMI-VPy were in the *trans* conformation. Under UV irradiation, the AZO units were transformed into the polar *cis* conformation and thus made the AZOMI-VPy aggregation. In the meantime, macroscopic precipitation was inhibited by the soluble CPB chains surrounding the AZOMI-VPy aggregates through hydrogen-bonding interaction. Thus, core-shell micelles were formed with a diameter of about 250 nm. Under irradiation with visible light, the micelles were quickly disassociated into interpolymer complexes as the AZO *cis* form returned to the *trans* form.

Interestingly, AZO units can also be introduced into the host-guest systems to build intelligent micelles and vesicles based on the self-assembly of stimuli-responsive block copolymers.[37,39,41-44] Recently, Zhou and coworkers have reported a novel Janus particle assembled from a supramolecular block copolymer (HBPO-*b*-HPG), which is constructed by the noncovalent coupling between a hydrophobic hyperbranched poly(3-ethyl-3-oxetanemethanol) (HBPO) with an apex of an AZO group and a hydrophilic hyperbranched polyglycerol (HPG) with an apex of a β-cyclodextrin (CD) through the specific AZO/CD host-guest interaction **(Fig. 2).** As we know, AZO groups can undergo light-triggered

reversible isomerization between *trans*- and *cis*-forms under alternating visible and UV light irradiation. Only *trans*-AZO can form host-guest inclusion with CD, whereas *cis*-AZO cannot. In this system, such an amphiphilic supramolecular copolymer resembles a tree together with its root very well in the architecture, which self-assembles into unilamellar bilayer vesicles with narrow size distribution. Under the irradiation of UV light for 15 min, the HBPO-*b*-HPG polymer solution is transformed from turbid to transparent. Meanwhile, some yellow precipitates are observed, attributing to the insoluble *cis*-AZO-*g*-HBPO. In addition, the obtained vesicles can further aggregate into colloidal crystal-like close-packed arrays under freeze-drying conditions.[43]

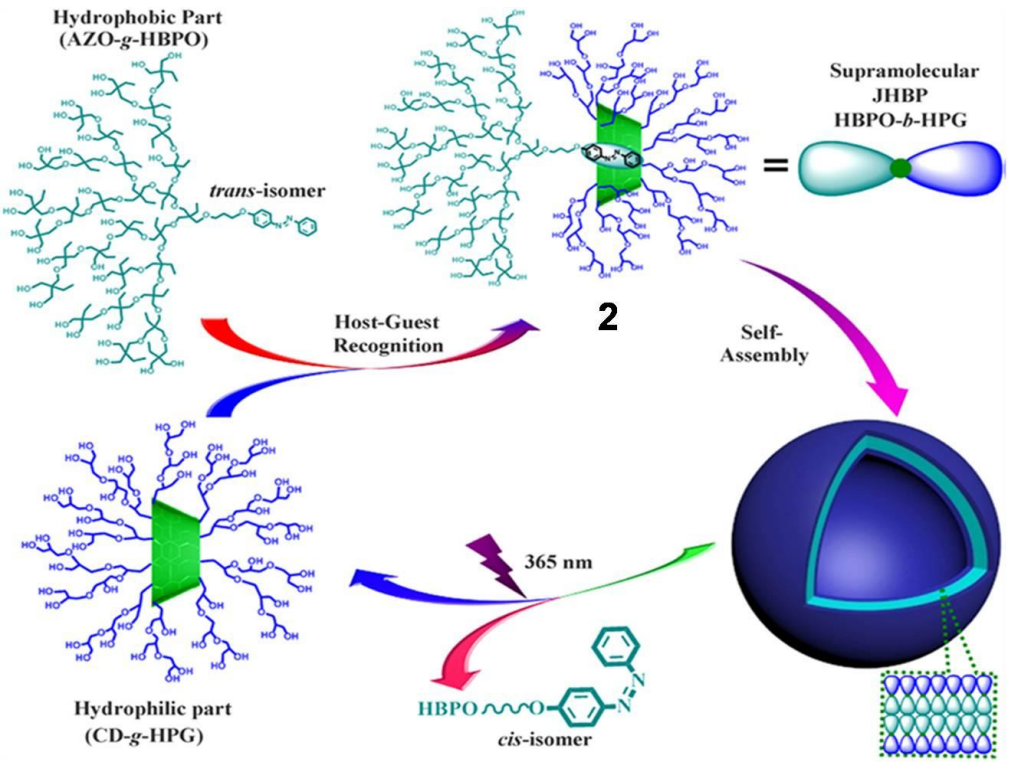


Fig. 2 Schematic illustration of the preparation, self-assembly and disassembly processes of the supramolecular block copolymer **2** and correspondent Janus particle after photoisomerization. Reproduced from ref. 43. Copyright 2013 American Chemical Society.

Combining light with other stimuli significantly broadens the scope of applications of such AZO-containing photoisomerization systems. Inspired by the jellyfish's breathing and light-emitting behavior **(Fig. 3a)**, a pH responsive polymeric vesicle with on-off switchable fluorescence was designed by Zhou and Zhu *et al*.[37] The polymeric vesicles were prepared through the aqueous self-assembly of an amphiphilic diblock copolymer consisting of abundant fluorescent chromophores of dimethylamino-azobenzene (DMA-AZOs) **(Fig. 3c)**, which could expand and shrink reversibly at different pH values accompanied with their wall thickness

variation. Furthermore, the vesicles exhibited aggregation-induced emission behavior in aqueous solution that led to strong fluorescence in the shrinking state and fluorescence quenching in the expanding state **(Fig. 3b)**. The occurrence of changes in the light-emitting properties of the polymeric vesicles upon membrane deformation during the breathing process was reminiscent of the breathing behavior of jellyfish. Therefore, they successfully develop a smart vesicle system with controllable and dynamic functions. More importantly, this study extends cytomimetic chemistry from the mere morphological transformation of membranes to a combination of cytomimetic morphology with the concomitant expression of a function.

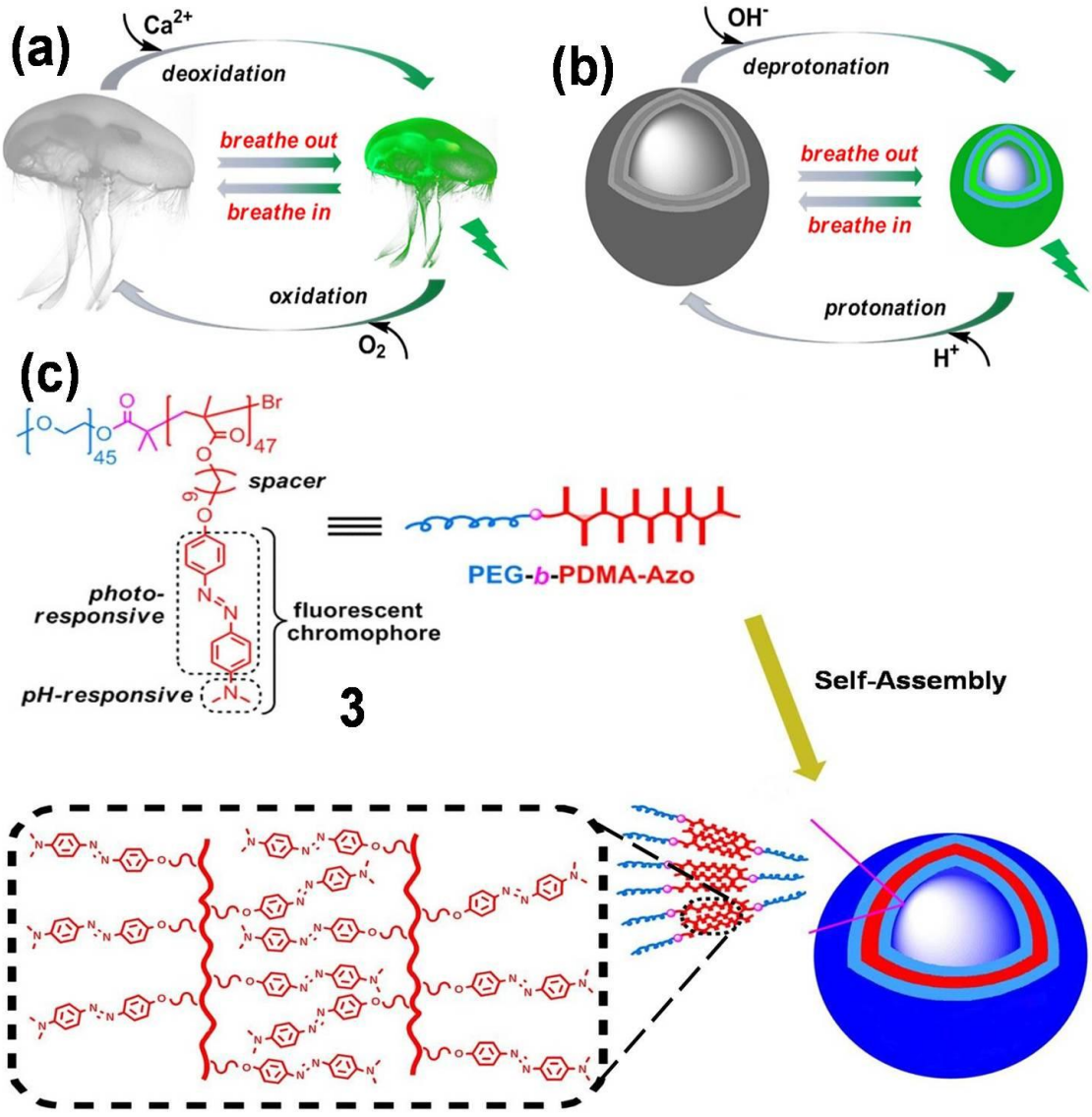


Fig. 3 Illustration of the breathing processes of (a) jellyfish and (b) vesicles accompanied by highly reversible green-fluorescence quenching and recovery. (c) Schematic representation of the amphiphilic diblock copolymer poly(ethylene glycol)-*block*-poly(dimethylamino-azobenzene) (PEG-*b*-PDMA-AZO) **3** and the vesicle structure. Reproduced from ref. 37. Copyright 2012 Wiley-VCH.

3.2 SP-containing photoisomerization micelles

SP is also a promising photoisomerization group that undergoes a reversible isomerization from the hydrophilic zwitterionic merocyanine state (so called open form) to the hydrophobic SP state (so called closed form) under visible light (620 nm) irradiation, while the reverse process is triggered by UV light (365 nm). The SP-containing polymers have been widely studied for various biomedical applications such as sensors, bioimaging, and drug delivery.[3,65,73] Comparing to AZO moieties, the incorporation of SP units into block copolymer micelles leads to reversible micelles with improved light responsiveness, since the difference in polarity between hydrophobic SP units and hydrophilic zwitterionic merocyanine units is greater.[74] In a typical example, Matyjaszewski and coworkers reported a poly(ethylene oxide)-*block*-poly(methacrylate) whose methacrylate block had SP side-chains (PEO-*b*-PMSP) (**Fig. 4**).[71] Micelle disruption was observed upon UV irradiation of the aqueous solution of PEO-*b*-PMSP micelles due to the photo-induced conversion of neutral SP to charged merocyanine. Besides, this system was successfully used for the encapsulation and release of a hydrophobic coumarin 102 dye, which was initially encapsulated in micelles made of the PEO-*b*-PMSP and then released upon excitation at 365 nm. Moreover, a portion of the released hydrophobic dye could be re-encapsulated into the regenerated micelles.

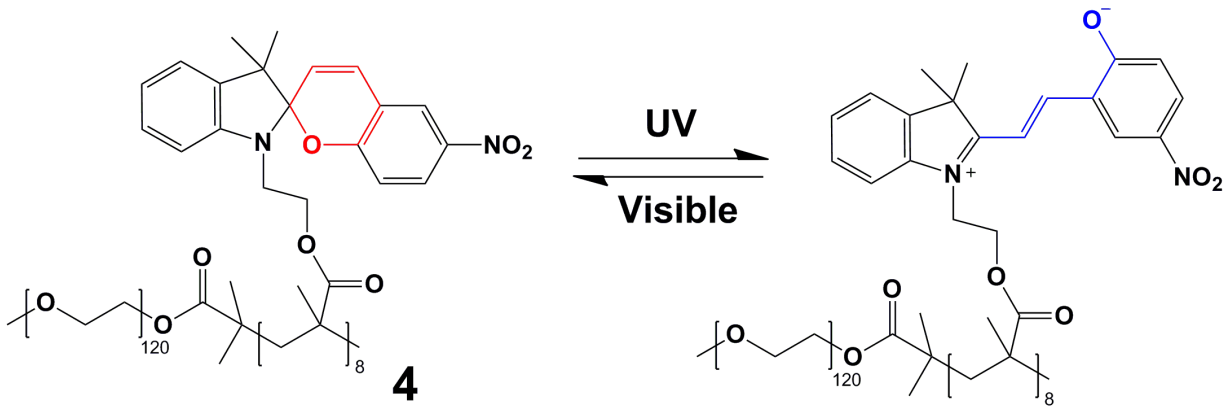


Fig. 4 Representative amphiphilic copolymers **4** bearing SP groups used for the reversible light-induced disruption or formation of aqueous micelles. Reproduced from ref. 71. Copyright 2007 Wiley-VCH.

Multi-responsive systems combining response to light and to another stimulus have also been successfully designed. An example is a copolymer with the SP-containing thermo-sensitive polymer having a lower critical solution temperature (LCST).[75] In this case, a photo and thermo double-responsive block copolymer is synthesized by atom transfer radical polymerization (ATRP) of a SP-containing methacrylate (SPMA) with di(ethylene glycol)

methyl ether methacrylate (DEGMMA). Owing to the existence of the photo-switchable PSPMA block and the thermo-responsive PDEGMMA block, both PSPMA-core and PDEGMMA-core micelles can be obtained by adjustment of the solution temperature and photo irradiation. Under visible light irradiation at 15 ^{o}C, the block copolymer self-assembles into PSPMA-core micelles. In contrast, under UV light irradiation at 30 ^{o}C, PDEGMMA-core micelles are formed. This double-responsive micelle system is also successfully used as nanocarriers to the efficient encapsulation, triggered release, and partial re-encapsulation of model coumarin 102 dye.

3.3 DTE-containing photoisomerization micelles

Among the various families of photoisomerization groups, DTE is versatile. DTE and its derivatives not only have very high thermal barriers to isomerization in the absence of light, but also show predictable conformational shape and rigidity changes between ring-open and ring-closed photoisomers.[76-78] The DTE-containing photoisomerization micelles were achieved by Branda and coworkers. They synthesized a novel amphiphilic copolymer that was composed of a hydrophilic thermoresponsive poly(*N*-isopropylacrylamide) (PNIPAM) backbone decorated with hydrophobic photochromic DTE components. In aqueous conditions, this copolymer self-assembled into nano-micelles capable of reversibly responding to two external stimuli (light and temperature) (**Fig. 5**).[72]

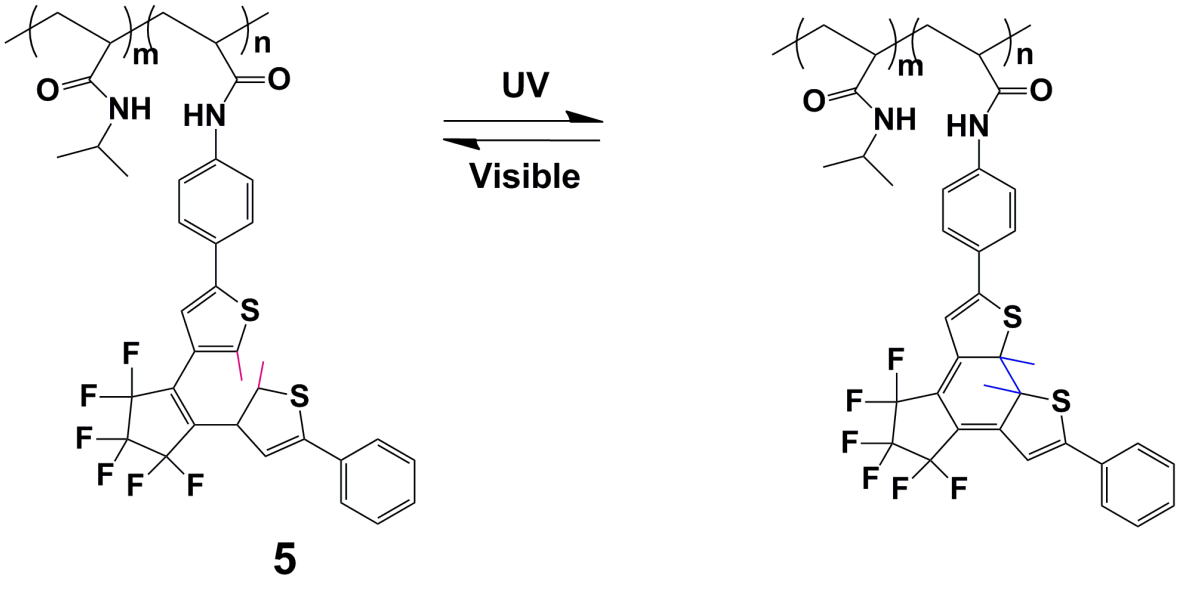


Fig. 5 Representative amphiphilic copolymers **5** bearing DTE groups used for the reversible light-induced disruption or formation of aqueous micelles. Reproduced from ref. 72. Copyright 2011 Elsevier.

As stated above, photoisomerization is a molecular behavior in which structural change between isomers is caused by UV/visible light. Clearly, upon the alternating irradiation with UV and visible light, the micelle disruption and formation can be reversibly induced by adjusting the hydrophilicity-hydrophobicity balance in photoisomerization polymeric micelle system.

4. Photo-induced rearrangement polymeric micelles

Photo-responsive polymeric micelles have the ability to encapsulate and retain hydrophobic drugs in their interior, which have found potential use in a wide range of biomedical applications. Under exposure to a specific light, the hydrophobic segment of amphiphilic polymers converts into hydrophilic one, resulting in the disassembly of polymeric micelles. As a typical photo-trigger group, the hydrophobic 2-diazo-1,2-naphthoquinone (DNQ) molecule can be changed into hydrophilic 3-indenecarboxylic acid (3-IC) molecule with a pKa of 4.5 through UV-induced Wolff rearrangement reaction (**Fig. 6a**).[79-82] More importantly, Urdabayev and Popik recently have demonstrated that DNQ can also undergo the same Wolff rearrangement *via* a two-photon process under near infrared (NIR) laser light.[83] Because of their interesting photo-induced rearrangement features, a number of photo-responsive micelles based on DNQ-containing polymers have been explored.[84,85] Fréchet and coworkers used unharmful NIR light to photo-activate a DNQ-based micellar system to release Nile red dyes.[86] In their design, a PEG-lipid conjugate terminated with DNQ could assemble into micelles (**Fig. 6b**). Upon irradiation of the micellar solutions with 795 nm light, the DNQ underwent a Wolff rearrangement to generate 3-IC, thereby transforming the hydrophobic DNQ into a hydrophilic moiety. However, this system had a relatively high critical micelle concentration (CMC) and exhibited a rather high cytotoxicity. In order to reduce both the CMC and the cytotoxicty of this micellar system, they further developed a poly(ethylene oxide) (PEO)-*block*-[G4] dendritic polyester copolymer functionalized with DNQ groups at its periphery (**Fig. 6c**).[87] This new system exhibited a lower CMC of 12 μg/mL and little cytotoxicity even at the concentration up to 1 mg/mL. The resultant micelles were capable of effectively delivering a hydrophobic payload triggered by NIR.

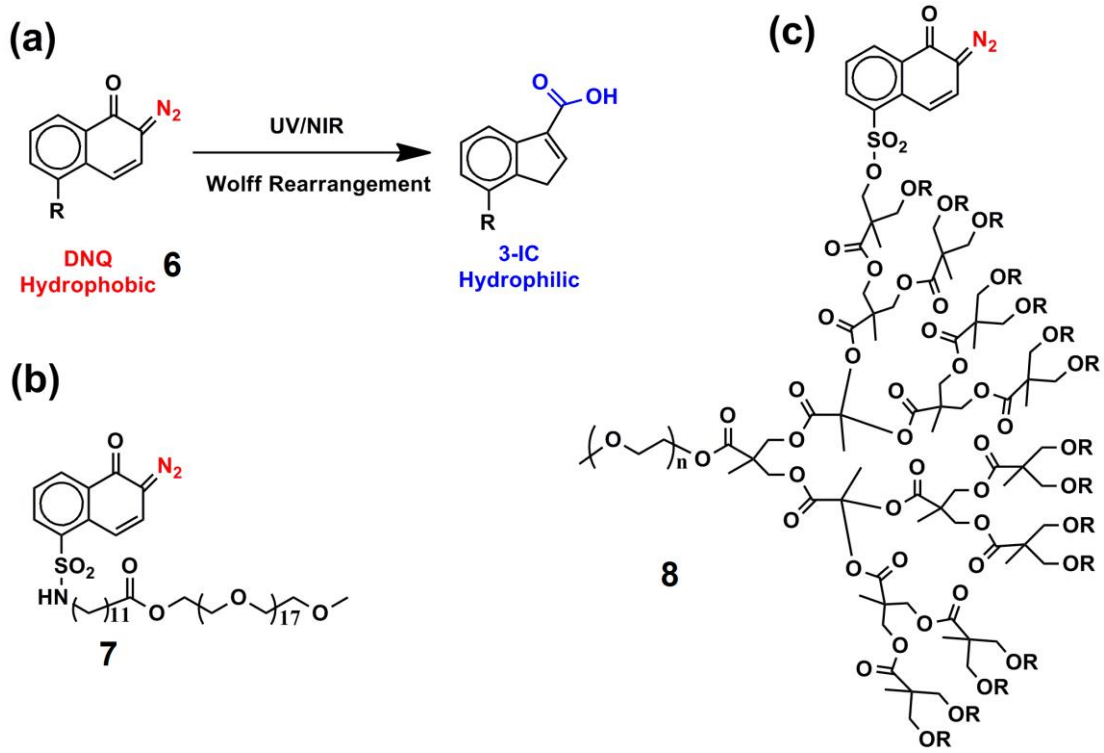


Fig. 6 Illustration of (a) the solubility change in DNQ derivatives **6** after photo-induced Wolff rearrangement, (b) linear DNQ-PEO amphiphile **7**; (c) linear-dendritic DNQ-decorated PEO-*b*-G4-polyester **8**. Reproduced from ref. 87. Copyright 2007 Royal Society of Chemistry.

It is important that the photoreaction of drug-loaded micelles is induced by NIR light for enhancing intracellular release of anticancer drugs. Very recently, Ji and coworkers reported a NIR light-sensitive polymeric micelle for the enhanced intracellular delivery of doxorubicin (DOX).[88] The micelles were formed from an amphiphilic copolymer (Dex-DNQ) synthesized by modification of hydrophilic dextran (Dex, a highly water-soluble polysaccharide with excellent biocompatibility and non-fouling properties[89-92]) with hydrophobic DNQ molecules. Under NIR laser irradiation, the dissociation of these biocompatible micelles occurred due to the Wolff rearrangement reaction of DNQ molecules. Correspondingly, the encapsulated DOX would be triggered to release into cancer cells after the endocytosis of DOX-loaded micelles by tumor cells. This smart drug carrier undoubtedly could be potentially used for cancer chemotherapy.

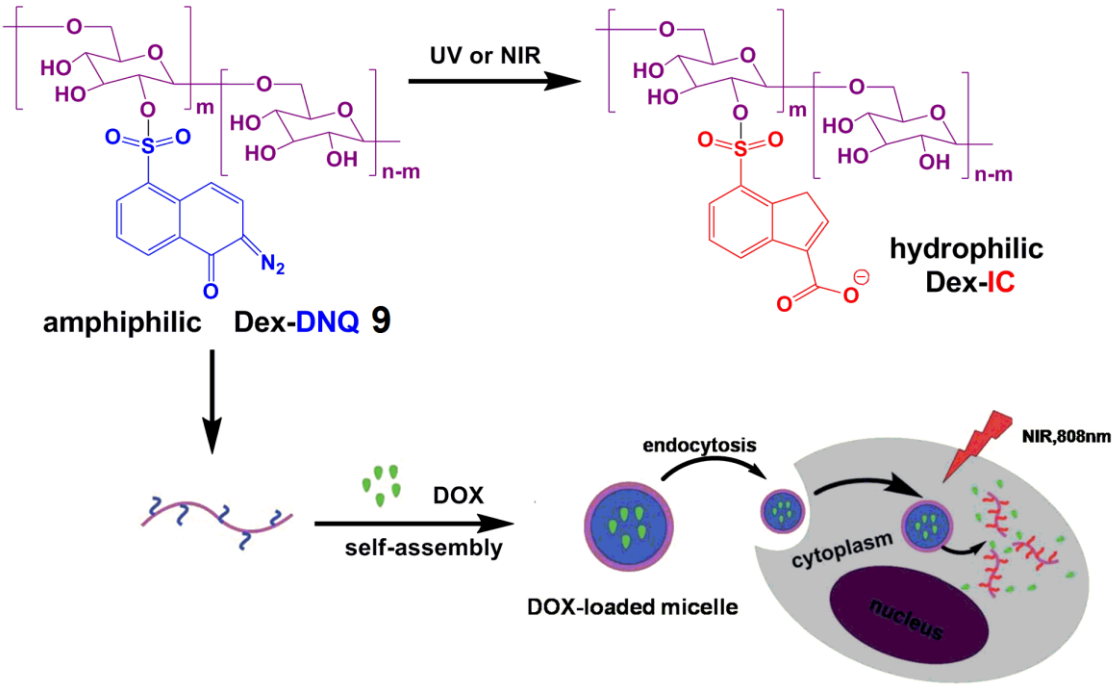


Fig. 7 Illustration of self-assembly and photo-induced Wolff rearrangement of amphiphilic Dex-DNQ copolymer **9**. The Wolff rearrangement of the DNQ molecules upon NIR irradiation will result in the dissociation of the micellar structure and enhancement of the intracellular release of DOX. Reproduced from ref. 88. Copyright 2012 Royal Society of Chemistry.

As the aforementioned DNQ-containing micelles lack highly efficient tumor-targeting properties,[53,84,86-88] the development of the nanocarriers that simultaneously exhibit NIR-sensitivity and active targeting effect might enhance the intracellular uptake and drug efficacy. By using click chemistry, Dong and coworkers modularly synthesized a class of degradable and dendritic sugar-focal-point and DNQ-decorated poly(amidoamine)-*block*-poly(3-caprolactone) (PAMAM-*b*-PCL) amphiphiles **(Fig. 8)**, which self-assembled into spherical micelles.[85] After 10 min of 365 nm irradiation, most of the micelles disappeared, confirming the light-triggered disruption of the micelles. Utilizing hydrophobic anticancer drug DOX as a model, *in vitro* drug-release profiles of the DOX-loaded nanomedicines showed that the DOX release became faster with increasing the irradiation time.

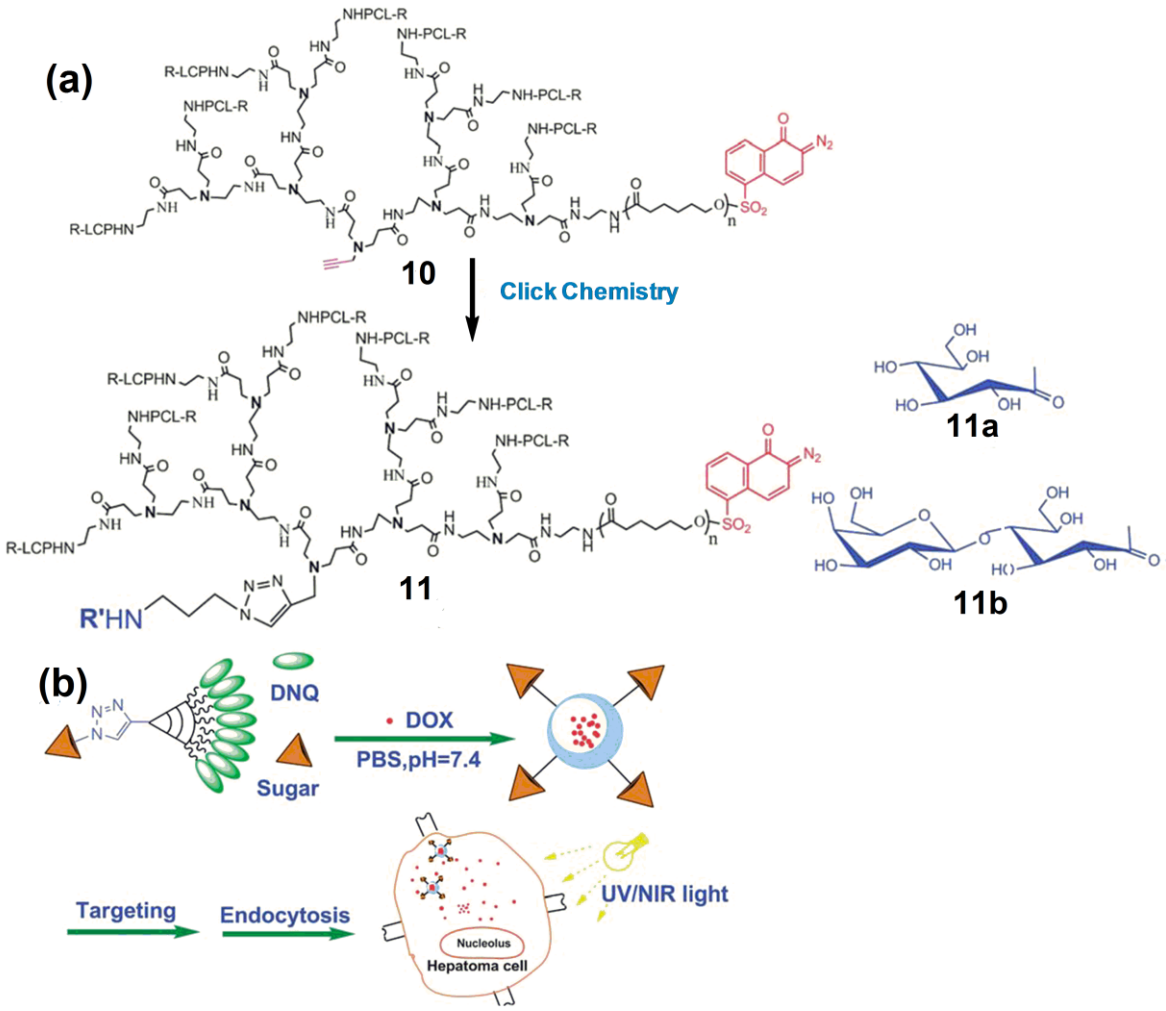


Fig. 8 Illustration of (a) the synthesis of degradable and dendritic PAMAM-*b*-PCL amphiphiles **11**; (b) the self-assembled DOX-loaded nanomedicines, the sugar-triggered targeting to cells, and the UV/NIR-sensitive drug-release. Reproduced from ref. 85. Copyright 2011 Wiley-VCH.

Besides their excellent drug-encapsulation properties and multivalent characteristics, Janus dendritic scaffolds constituted of two chemically distinct dendrons can self-assemble into multi-functional nanostructures.[53,93-101] Dong, Zhu and coworkers reported an amphiphile D*m*-Lac-D3DNQ, which was synthesized by connecting hydrophobic DNQ-decorated PAMAM dendron D3 (generation 3) and hydrophilic lactose (Lac)-decorated PAMAM dendrons D*m* (*m* = 0, 1, and 2) *via* click chemistry **(Fig. 9a)**.[38] The Janus-type amphiphile D*m*-Lac-D3DNQ self-assembled into the DNQ-cored micelles dangled by densely free Lac groups in aqueous solution. Making use of DOX as a model, the disruption of the micelles was accompanied by the release of the DOX *via* UV/NIR irradiation **(Fig. 9b)**. Significantly, this work provides a versatile strategy for the fabrication of NIR-responsive and lectin-binding

dendrimer nanomedicine, opening a new avenue for "on-demand" and spatiotemporal drug delivery.

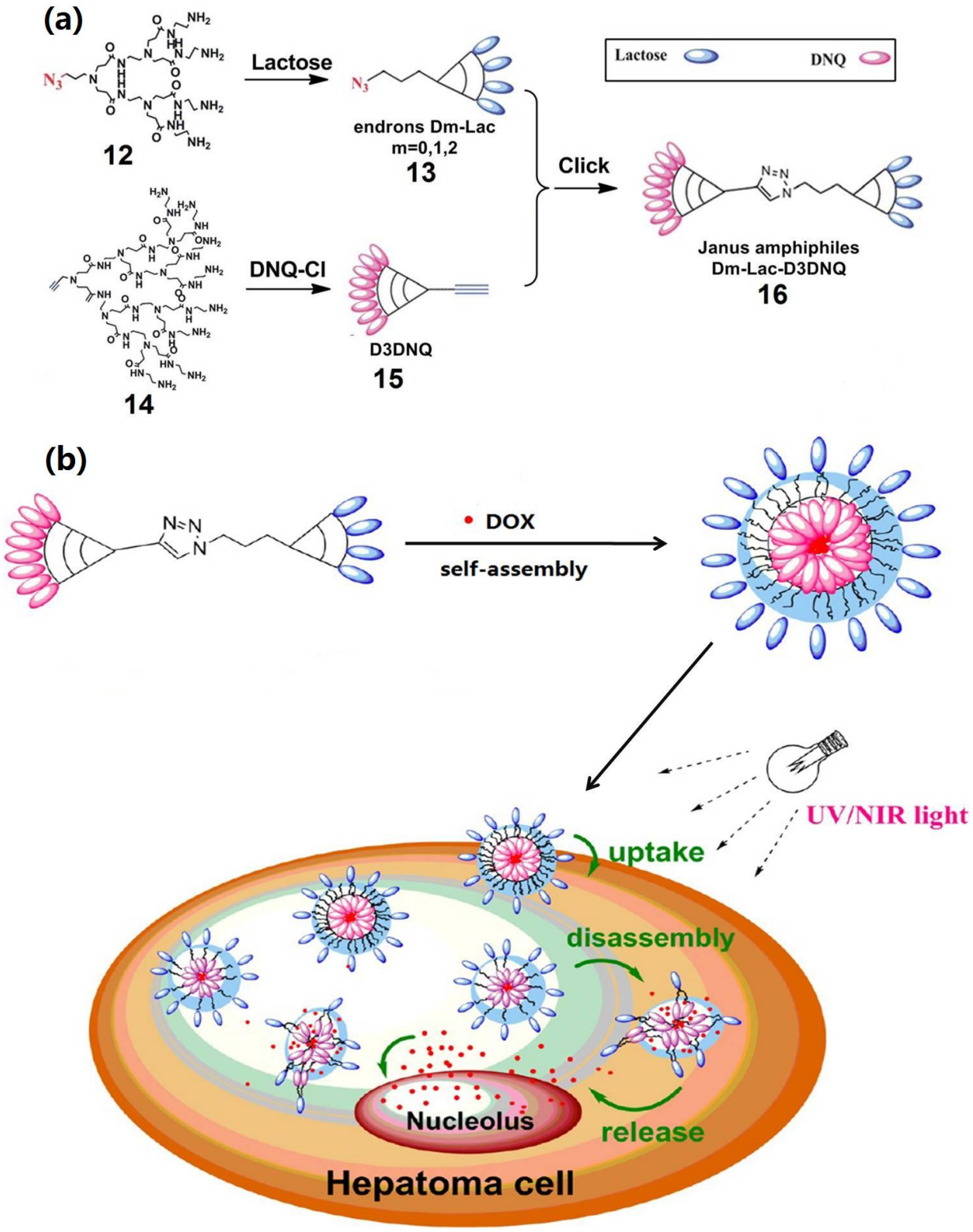


Fig. 9 Illustration of (a) the synthesis of Janus-type PAMAM amphiphiles D*m*-Lac-D3DNQ **16** by click chemistry; (b) the self-assembled DOX-loaded nanomicelles of **16**, the cellular uptake, and the UV/NIR-sensitive disassembly and DOX release inside the cells. Reproduced

from ref. 38. Copyright 2012 American Chemical Society.

5. Photocleavage polymeric micelles

The photocleavage reaction that occurs in the photochromic *o*-nitrobenzyl (NB) and coumarin incorporated copolymers is found to be another efficient mode for constructing photo-responsive polymeric micelles.[52,53,65,102] The photocleavage groups can be located in the side chain, the main chain or the middle block junction of copolymers, as shown in **Fig. 10**.[51-53] Apparently, these three classes of copolymers have different light-sensitive characteristics, which may result in different modes of micellar disruption and cargo release. In regard to the photochromic side chain copolymers, the hydrophobic photochromic block transforms into a hydrophilic one after irradiation, leading to partial or complete disruption of micelles and the concomitant cargo release. As for the photochromic main-chain polymers, the polymer backbone breaks into oligomers or small molecules under irradiation, resulting in a fast degradation and complete micellar disruption that allows for the burst release of the payloads. With respect to the copolymers incorporated with one photochromic junction, they are split into two distinct polymer chains upon irradiation, causing the re-organization of hydrophobic micellar cores (*e.g.*, forming bigger aggregates) or the morphological transition (*e.g.*, from vesicles to micelles), and an encapsulated cargo release profile may simultaneously occur.

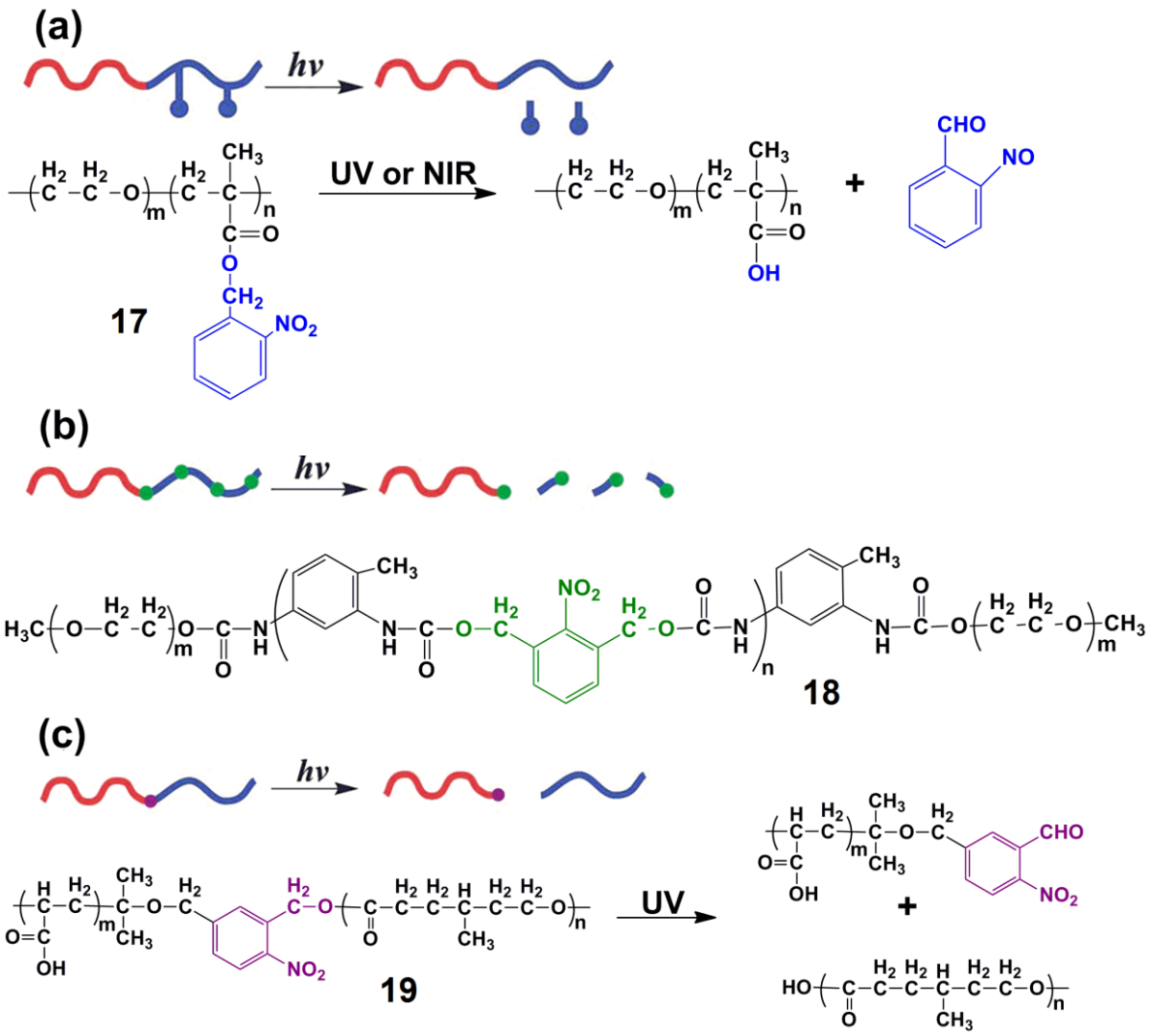


Fig. 10 Illustration of the photocleavage reaction and examples of copolymers containing NB group **17-19** based on each type of design in (a-c) the side chain, main chain, and junction point of photochromic copolymers, respectively. Reproduced from ref. 51. Copyright 2012 American Chemical Society.

5.1 NB-containing photocleavage polymeric micelles

The NB-bearing polymers are extensively studied because NB and its derivatives are expediently available or easy to synthesize in laboratory. Moreover, the photolysis process of NB can be triggered *via* either one-photon UV light and/or two-photon NIR light.[103] Recently, increasing efforts have been made to study amphiphilic NB side chain copolymers. In this respect, Zhao and coworkers described the synthesis of diblock copolymers containing one hydrophilic poly(ethylene oxide) (PEO) sequence linked to a hydrophobic poly(methacrylate) (PMA) block bearing photocleavage side groups (**Fig. 11**).[40,48,104,105] Different types of photocleavable blocks have been introduced *via* ATRP, including *o*-nitrobenzyl esters,[104] pyrenylmethyl esters,[40] and esters of (diethylamino)-methylcoumarinyl.[105] These block

copolymers formed micelles in water with a PEO shell and a PMA core, which further loaded with hydrophobic drug molecules. Light irradiation induced the cleavage of the side chromophores, producing a poly(methacrylic acid) (PMAA) block. As the resulting PEO-*b*-PMAA was fully hydrophilic, the disruption of the original micelles and the release of the encapsulated drug molecules were clearly observed.

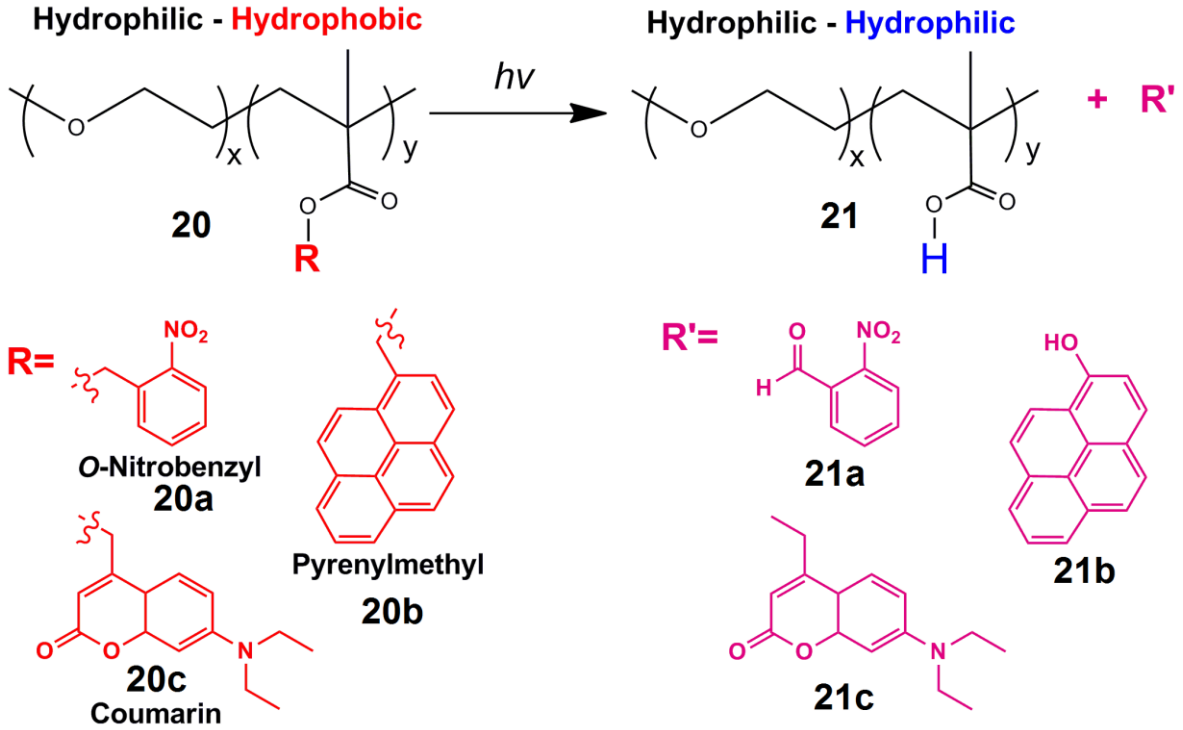


Fig. 11 Representative photocleavage groups employed for the irreversible light-induced disruption of aqueous micelles: *o*-nitrobenzyl **20a**, pyrenylmethyl **20b**, and coumarin **20c**. Reproduced from ref. 48. Copyright 2013 Royal Society of Chemistry.

Although amphiphilic photocleavage side-chain copolymers can be easily synthesized by controlled radical polymerization, the weakness is that the water-soluble photoproduct is not degradable. This certainly limits its clinical applications as the photoproduct cannot be discharged from the body. Thus, the design of biodegradable and biocompatible light-responsive polymers sounds particularly important. Dong and coworkers have designed a novel NB-functionalized α-amino acid *N*-carboxyanhydride (NCA) monomer and synthesized a series of photo-responsive polypeptide block copolymers PEO-*block*-poly(S-(*o*-NB-*L*-cysteine) (PEO-*b*-PNBC).[45] The PEO-*b*-PNBC self-assembled into spherical micelles with an average size of about 79 nm, which became smaller and then kept constant at 44 nm after 30 min of 365 nm irradiation, presenting a photo-responsive self-assembly and DOX-release properties **(Fig. 12)**. This work develops a versatile platform, not only for the synthesis of photo-responsive polypeptide block copolymers but for the

fabrication of biodegradable and biocompatible photo-responsive polymeric nanomicelles.

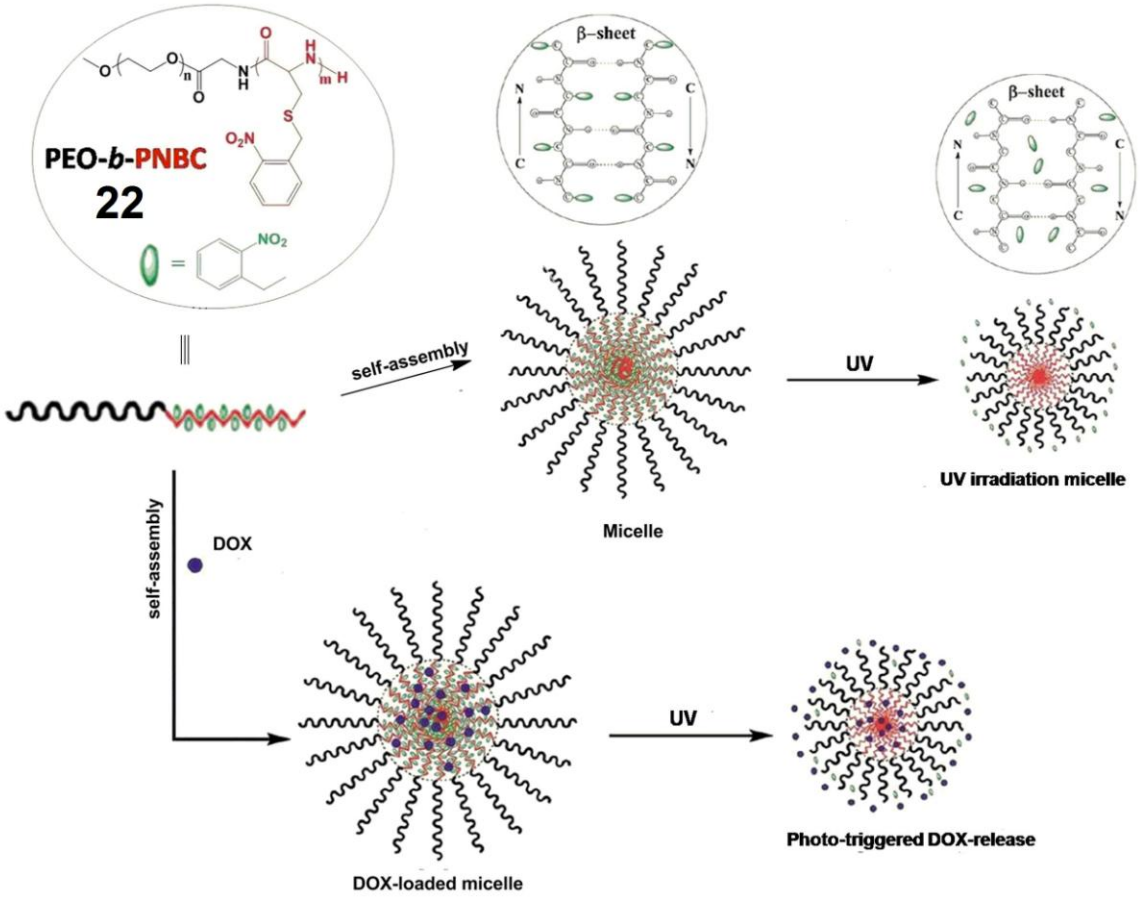


Fig. 12 Illustration of photo-responsive self-assembly and photo-triggered DOX-release of the amphiphilic PEO-*b*-PNBC block copolymers **22** in aqueous solution. Reproduced from ref. 45. Copyright 2012 American Chemical Society.

5.2 Coumarin-containing photocleavage polymeric micelles

The coumarin family has thousands of different derivatives, and exhibits wide range of application prospects in polymer science, biomaterials, and biology as well.[106] With respect to photocleavable coumarin-containing micelles, Zhao and coworkers reported a NIR-sensitive amphiphilic block copolymer composed of PEO and poly-(7-diethylaminocoumarin-4-yl-methyl methacrylate) (PDEACMM) (**Fig. 13a**).[53,105] Under UV or NIR irradiation, the photosolvolysis of 7-diethylamino-coumarin-4-yl-methyl esters resulted in the cleavage product DEACMM, and the hydrophobic PDEACMM block was converted to hydrophilic PMMA. Meanwhile, under exposure to the NIR for 285 min, micelles appeared to be highly degraded and their disruption was sufficient to release loaded Nile red. In order to enhance the biocompatibility and biodegradability of copolymer micelles, they further designed a class of NIR responsive PEO-*block*-polypeptide copolymer (PEO-*b*-PLGA-*co*-COU), in which the polypeptide poly(L-glutamic acid) block was linked

with photochromic 6-bromo-7-hydroxycoumarin-4-yl-methyl groups (**Fig. 13b**).[53,107] Upon UV or NIR irradiation, the photocleavage reaction of coumarin moieties converted the photochromic polypeptide block into the relatively hydrophilic poly(L-glutamic acid), causing the disruption of the copolymer micelles. Moreover, a significant amount of drug molecules could be released from the micelles upon NIR irradiation for 220 min. However, upon NIR irradiation, the photocleavage reaction time for the coumarin-containing micelles was too long to on-demand drug delivery. Simultaneously, the study of coumarin-containing polymeric nanomedicines was very limited probably due to the complex synthesis of photocleavable coumarin derivatives compared with commercial NB derivatives. Therefore, the comparative researches on the coumarin-containing polymeric micelles still have a long way to go in the future.

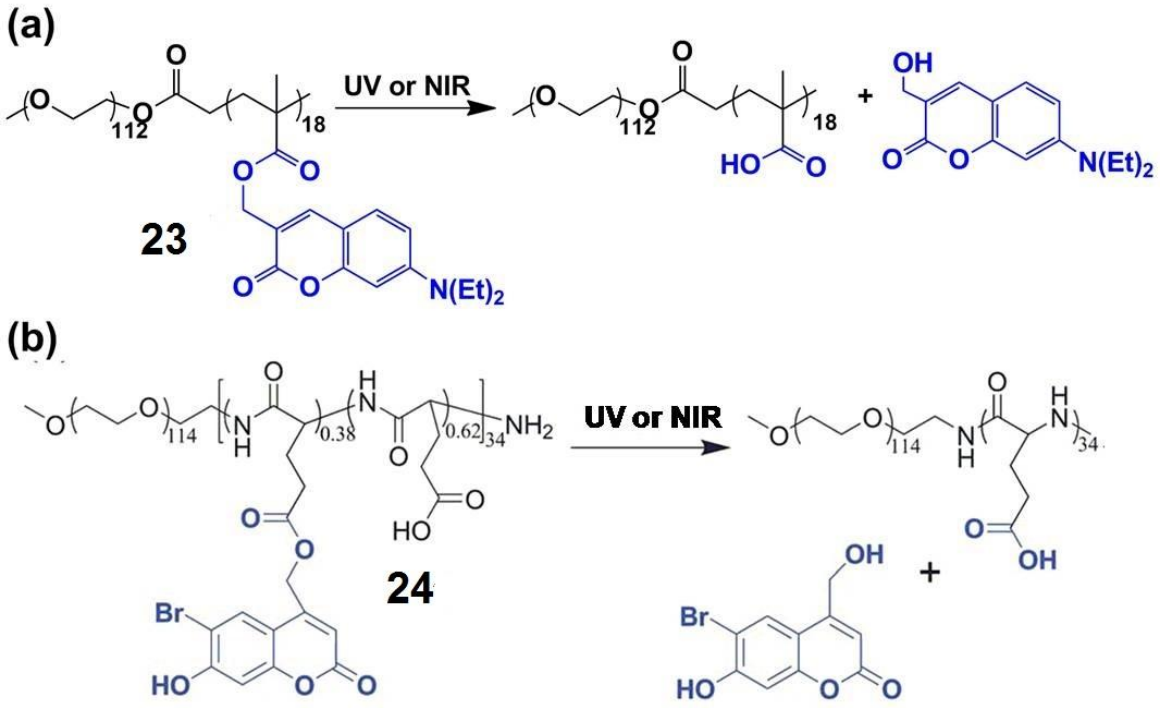


Fig. 13 Illustration of (a) PEO-*b*-PDEACMM copolymer micelle **23** and its photo-induced cleavage reaction; (b) PEO-*b*-PLGA-*co*-COU copolymer micelle **24** and its photo-triggered cleavage reaction. Reproduced from ref. 53. Copyright 2013 Royal Society of Chemistry.

6. Photo-induced crosslinkable polymeric micelles

It is well-known that the major drawback of micelles is their dynamic nature which leads to instabilities at high temperature, at low concentration and under certain changes in solvent conditions. As a result, there has been significant interest in the stabilization of micelles and in particular, polymer micelles. In nature, crosslinking is an easy and efficient approach to stabilize these micellar structures, which might be a prerequisite for some applications.[108]

Among the different methods allowing micellar crosslinking, light-induced crosslinking is a valuable tool since chemical reagents and unwanted byproducts are avoided.

6.1 Cinnamic ester-containing photo-induced crosslinkable micelles

Light-induced crosslinking of micelles was firstly reported by Liu and coworkers who used the [2+2] photocycloaddition of cinnamic esters for photo crosslinking.[109-111] In addition, a large amount of work were inspired from a well-studied photochemical system: the cinnamic acid-truxillic acid reversible photochemical [2+2] cycloaddition reaction. Cinnamic acid forms, under illumination with UV (λ>260 nm), a dimer, truxillic acid, which is stable at elevated temperature and under a wide range of wavelengths of UV light. However, the cyclobutane ring of truxillic acid is photolabile under deep-UV light (λ<260 nm), giving back the original cinnamic acid.[112-114] In this case, a typical example illustrating this system was shown in **Fig. 14** in which the micelles were formed by the self-assembly of polystyrene-*block*-poly(2-cinnamoylethyl methacrylate) (PS-*b*-PCEMA) with PCEMA shell and PS core in tetrahydrofuran/acetonitrile (THF/AN, 1/9, *v*/*v*).[111] Upon photolysis, the PCEMA micellar shell was subsequently cross-linked. Despite the PCEMA shell, the degree of intermicellar fusion was low with CEMA conversions less than ~40%. The micellar structures, with greater than ~10% CEMA conversions, were dispersible and structurally stable in THF and toluene, solubilizing both PS and un-cross-linked PCEMA. Moreover, Liu and coworkers recently have reported a triblock terpolymer poly(ethyleneoxide)-(*o*-nitrobenzyl)-poly[2-(perfluorooctyl)ethyl-meth-acrylate]-*block*-poly(2-cinnamoyloxyethylmethacrylate) (PEO-ONB-PFOEMA-*b*-PCEMA).[115] In their system, PEO was water-soluble, PCEMA was photo-cross-linkable, PFOEMA was of low surface tension, and ONB denoted a photocleavable NB unit at the junction of the PEO. Micelles were formed from this copolymer in THF/water mixture (1/4, *v/v*), in which only the PEO block was soluble. After photolyzing the sample with UV light, the micellar PCEMA cores were cross-linked and then the PEO blocks were released into solution, resulting in the precipitation of cross-linked PFOEMA-*b*-PCEMA nanoparticles.

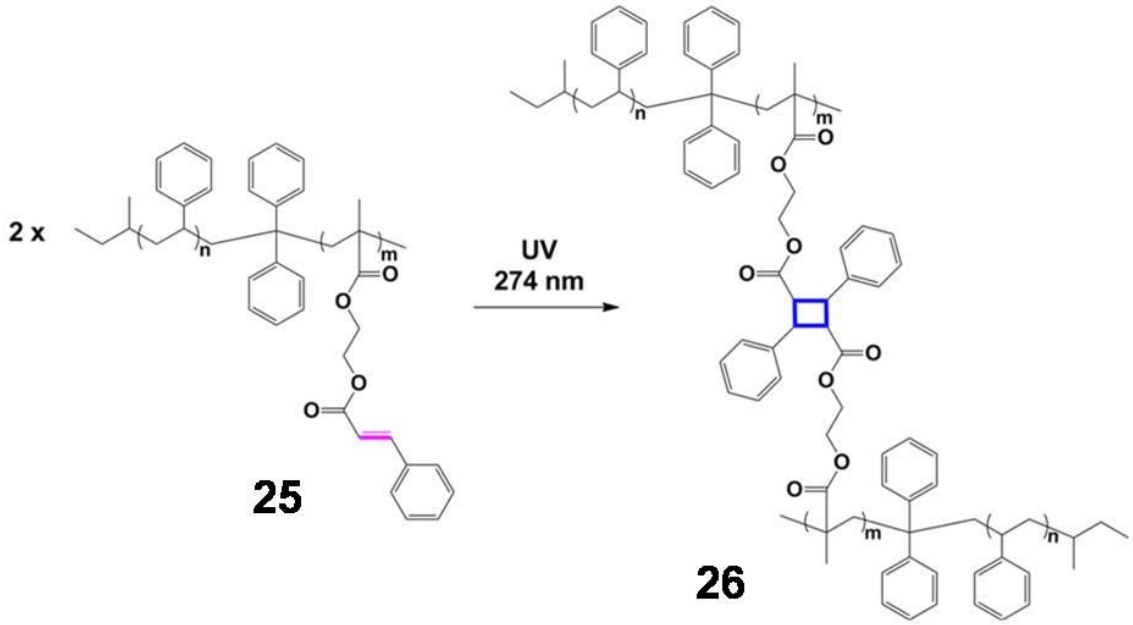


Fig. 14 Photo-dimerization of cinnamic esters **25**. Reproduced from ref. 111. Copyright 1998 American Chemical Society.

6.2 Coumarin-containing photo-induced crosslinkable micelles

Coumarin is another promising category of photo-induced crosslinking groups. As an example, Saegusa *et al*. studied the reversible sol-gel transition of polyoxazolines.[116] The resulting polymer had degrees of coumarin substitution ranging from 1.2% to 30.4%. The photo-dimerization of the polymer was performed with a 450 W high-pressure Hg lamp for up to 3 h, while the photocleavage reaction was accomplished with UV irradiation (253 nm) for 2 h. This study was the first to demonstrate the photo-reversibility of crosslinking using coumarin groups. However, little work utilizing the reversible dimerization of coumarin in polymers to stabilize micelles was published. Zhao and coworkers introduced coumarin derivatives in amphiphilic block copolymers.[117,118] They used the [2+2] photocycloaddition of coumarin groups under UV irradiation to fabricate a novel series of amphiphilic diblock copolymers with a water-soluble PEO block and various hydrophobic block including poly(coumarin methacrylate) (PCMA) and a random copolymer of poly(methyl methacrylate) (PMMA) and PCMA. In both cases, the photo-dimerization of coumarin moieties was triggered by irradiating the micelles at wavelengths above 310 nm while de-crosslinking occurred upon irradiation at wavelengths below 260 nm. It is worthwhile to mention that light not only affords the stability of polymer micellar aggregates *via* photo-crosslinking, but also allows the release of encapsulated guest through photo-induced disruption of the micelles. Similarly, they also introduced additional stimuli-responsive character to photo-cross-linked micelles. A diblock copolymer (PEO-*b*-P(MEOMA-*co*-CMA)) composed of PEO and a

coumarin-containing poly(2-(2-methoxyethoxy)ethyl methacrylate) (P(MEOMA-*co*-CMA)) with temperature-responsive behavior was presented,[119] as shown schematically in **Fig. 15**. Core-cross-linked micelles could be readily achieved from this copolymer at T>LCST of the P(MEOMA-*co*-CMA) block through dimerization of coumarin side groups upon absorption of UV light (λ>310 nm) and then cooling the solution to T<LCST to obtain crosslinked water-soluble polymeric nanoparticles. Under irradiation of UV light (λ<260 nm), the reverse photocleavage of cyclobutane rings led to a reduction of the crosslinking density, so as to control the size of the polymeric nanoparticles.

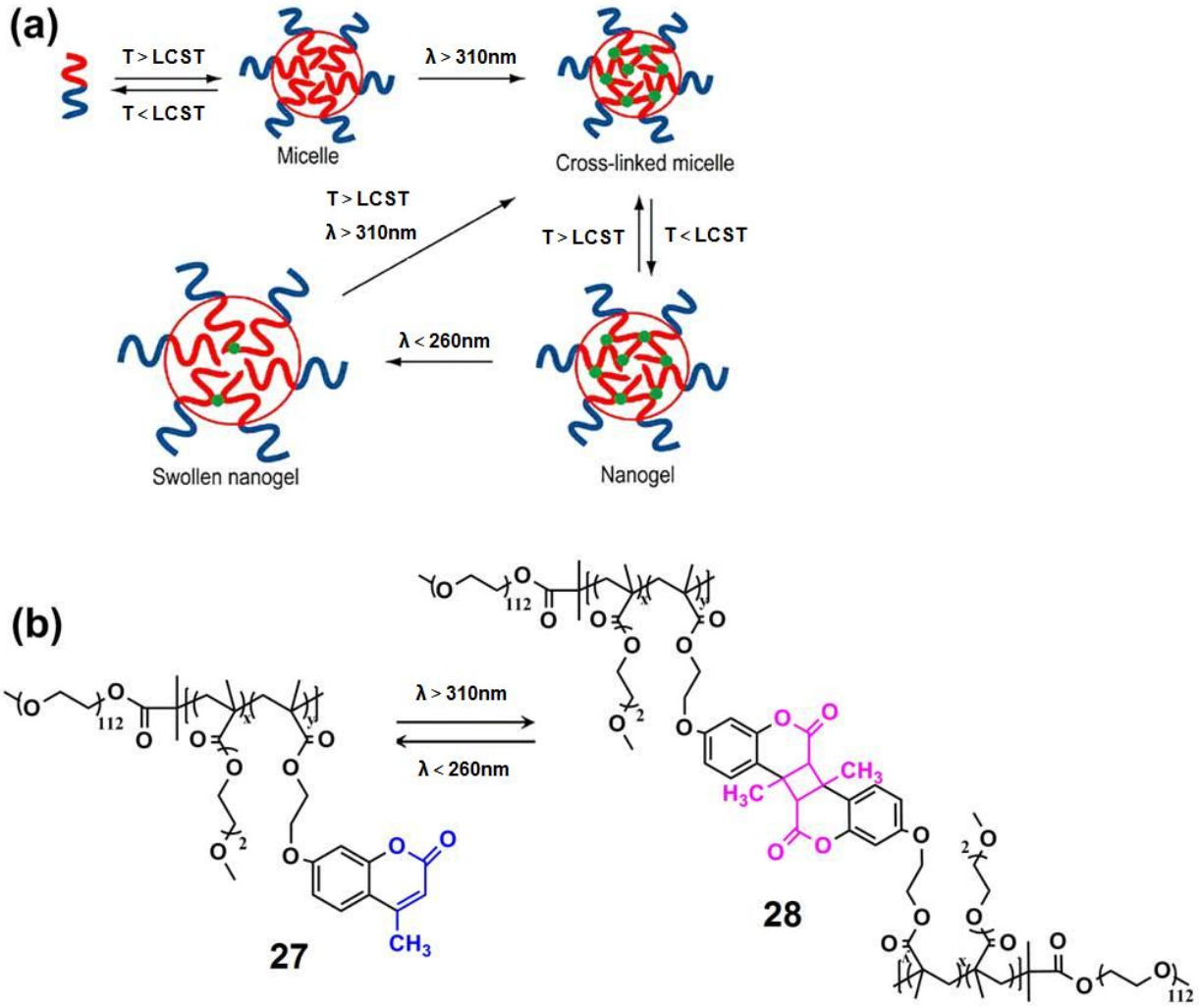


Fig. 15 Illustration of the copolymer **27** bearing coumarin side groups for the reversible photo-crosslinking reaction. Reproduced from ref. 119. Copyright 2009 American Chemical Society.

7. Photo-induced energy conversion polymeric micelles

The sunlight is the most important energy source for life on earth. Within one hour, more solar energy reaches our planet than the amount of energy that mankind consumes in one year. The

quality of life on earth strongly depends on accessible energy sources. However, we are running out of fossil fuels. In order to meet our future energy needs, therefore, it is urgently necessary to develop materials or devices that are able to collect and convert the energy of the sunlight or other kinds of light in a usable form. One of the most important biological processes is photosynthesis. The genesis of the photosynthetic apparatus was an essential step forward in the evolution of life on earth. In the course of evolution, bacteria and plants developed biological systems for the conversion of solar energy into chemical energy. For mimicking photosynthesis to convert the energy of the light into other types of energy, over the last few decades, attempts have been made by the researchers all over the world.[120-123]

After absorbing light energy, materials convert light energy directly into mechanical work (the photomechanical effect), resulting in the change of their shape or volume. In this case, it could be very efficient as a single-step energy conversion. It is well known that when AZO derivatives are incorporated into liquid crystals (LCs), the LC-isotropic (I) phase transition can be induced isothermally by irradiation with UV light to cause *trans-cis* photoisomerization, and the I-LC reverse-phase transition by irradiation with visible light to cause *cis-trans* back-isomerization. This photo-induced phase transition (or photo-induced reduction of LC order) has led successfully to a reversible deformation of LCs containing AZO units just by changing the wavelength of actinic light.[67,124-133] Recently, Ikeda and coworkers have prepared a continuous ring of the liquid-crystalline elastomer film by connecting both ends of the film.[134] The AZO units are aligned along the circular direction of the ring. Upon exposure to UV light from the downside right and visible light from the upside right simultaneously (**Fig. 16**), the ring rolls intermittently toward the actinic light source, resulting almost in a 360^{o} roll at room temperature. Successfully, light energy is ultimately converted into mechanical energy in this way.

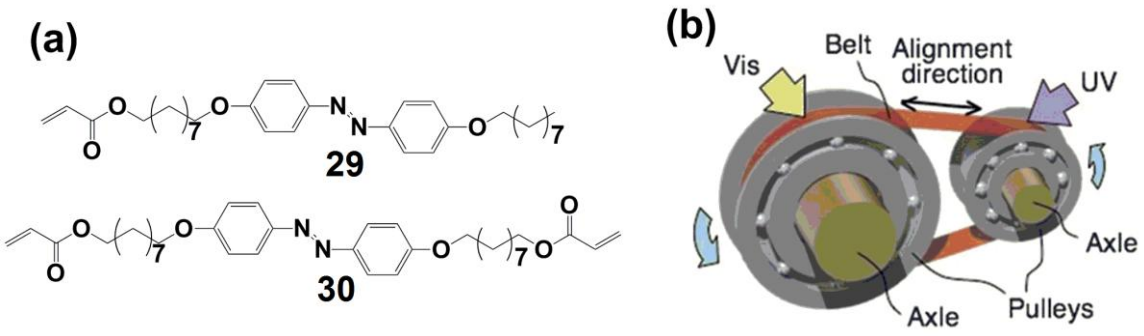


Fig. 16 (a) Illustration of the LC monomer **29** and LC diacrylate **30** structures. Upon cooling, **29** changes from an isotropic to a smectic phase at 92 ^{o}C, and at 60 ^{o}C it becomes crystalline; upon cooling, **30** changes from an isotropic to a smectic phase at 91 ^{o}C, and at 74 ^{o}C it becomes crystalline; upon cooling, the mixture of 1/2 (20/80 mol/mol) changes from an

isotropic to a smectic phase at 89 ^{o}C, and at 60 ^{o}C it becomes crystalline. (b) Schematic illustration of a light-driven plastic motor system and the relationship between light irradiation positions and a rotation direction. Reproduced from ref. 134. Copyright 2008 Wiley-VCH.

Besides the conversion from light energy to chemical or mechanical energy, specific wavelengths of light (*e.g.*, NIR light) can also be effectively converted into heat by using photo-thermal nanoparticles, such as gold nanoparticles.[135-139] As such, NIR-responsive nanoparticle platforms offer several important advantages for cancer therapy. For example, NIR-induced local heating can be used for cancer thermotherapy.[140,141] In addition, NIR-responsive nanoparticle delivery systems enable on-demand release of drugs for cancer chemotherapy, presumably by heat-induced disruption of the delivery vehicles.[135,136] Furthermore, the combination of NIR-based thermotherapy and triggered chemotherapy (thermo-chemotherapy) could provide higher therapeutic efficacy than respective mono-therapy.[142] Recently, Dai and coworkers have reported a gold-nanoshell-coated cholesterylsuccinyl silane (CSS) nanomicelle loaded with both DOX and Fe_3O_4 magnetic nanomicelle (CDF-Au-shell nanomicelle) to combine magnetic resonance (MR) imaging, magnetic-field-guided drug delivery, light-triggered drug release, and photothermal therapy (**Fig. 17**).[143] Fe_3O_4 magnetic nanoparticles loaded in nanomicelles show both MR imaging and magnetic-targeting functions. Gold nanoshells on the outer layer of nanomicelles operate as NIR-light-absorbing agents, which can thus result in effective NIR-triggered release of a drug to achieve photothermal therapy. Owing to light-to-heat transduction mediated by NIR irradiation of gold nanoparticles to generate a rapid rise in the local temperature, Farokhzad and coworkers have used DNA duplex as a drug loading scaffold.[144] The DNA duplex strands, which consist of sequential CG base pairs, provide loading sites for DOX, a DNA-targeting drug. Upon NIR laser illumination, DOX molecules are released at the target site for chemotherapy. The *in vivo* results show that the DNA-based platform effectively inhibits tumor growth through thermo-chemotherapy upon NIR laser irradiation after intratumoral injection. Very recently, Huang and coworkers have reported a relatively facile method for Au-nanorods (AuNRs) to deliver hydrophobic drugs. Paclitaxel (PTX) is loaded into a cetyltrimethylammonium bromide (CTAB) layer around as-synthesized AuNRs with high density (2.0×10^4 PTX per AuNR) *via* nonspecific adsorption.[145] Then, CTAB is replaced with PEG-linked 11-mercaptoundecanoic acid, which provides a hydrophobic pocket of the polymeric monolayer on the surface of AuNRs for PTX entrapment. The PTX-AuNR-enabled thermo-chemotherapy is found to be highly effective in killing three types of cancer cells, superior to photothermal therapy or chemotherapy alone due to a synergistic effect.

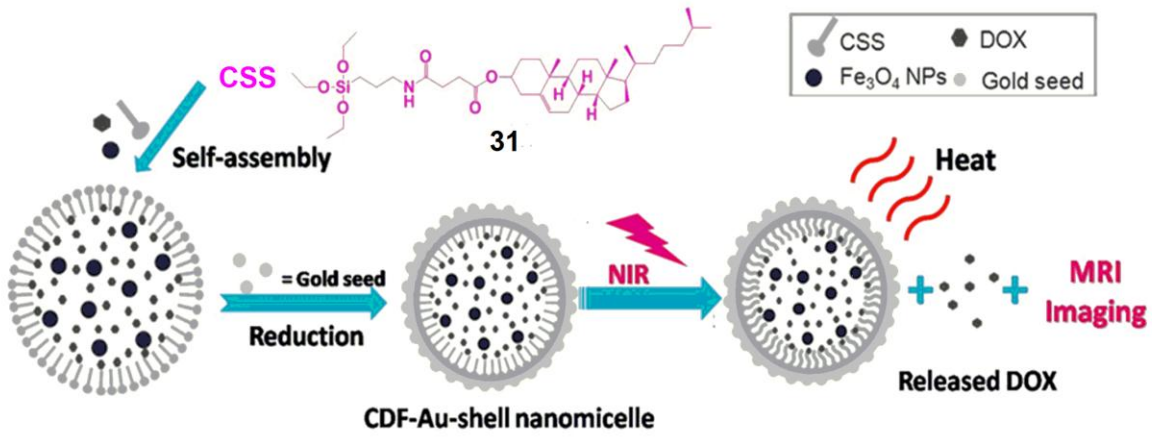


Fig. 17 Illustration of multifunctional CSS **31** nanomicelles as potential applications in cancer therapy. Reproduced from ref. 143. Copyright 2013 Wiley-VCH.

While looking back on the numerous previous literatures, to our knowledge, less attention has been paid on the design of photo-induced energy conversion polymers, particularly the photo-induced energy conversion polymeric micelle systems. Confidently, the photo-induced energy conversion (*e.g.* conversion from light energy to mechanical, thermal or other energy) polymeric systems will be the future directions in the intelligent material field.

8. Conclusion and Perspective

As highlighted in the previous sections, recent years have witnessed significant progresses in the field of photo-responsive polymeric micelles. We have classified the photo-responsive polymeric micelles into five categories based on the differences of photo-reaction mechanisms and the effect of light on each photo-responsive group, such as (1) photoisomerization polymeric micelles, (2) photo-induced rearrangement polymeric micelles, (3) photocleavage polymeric micelles, (4) photo-induced crosslinkable polymeric micelles, (5) photo-induced energy conversion polymeric micelles. Meanwhile, the light is not only able to cause the formation/disruption of the micelles by adjusting the hydrophilicity-hydrophobicity balance of the copolymers or using the photocleavage reaction, but also to stabilize the micellar structures by crosslinking. In addition, light energy can also be converted into mechanical or thermal energy for the special photo-responsive groups. It is clear that one of the key applications of photo-responsive polymeric micelles is their use as nanocarriers for controllable biopharmaceutical delivery. However, in regard to this field, there are still several major issues, which need to be solved currently. First, the biocompatibility and biodegradability of the selected photo-responsive polymers should be further improved. Up to now, while looking back on all the previous examples discussed in this review, PEG/PEO has been mostly considered as the hydrophilic blocks attributed to the fact that PEG/PEO is a biocompatible

polymer. However, less attention has been paid on the selection of the hydrophobic blocks. In this respect, some recent studies proposed the use of poly(amino acid) sequences modified by photocleavable moieties as hydrophobic blocks for photo-responsive polymers. The copolymer composed of a PEO block and a poly(glutamic acid) sequence, assembling micelles in aqueous medium that could be reversibly disassembled and reassembled upon irradiation to UV and visible light, respectively.[146] Second, the toxicity of the products might result from the photo-induced reactions. For example, the photo-degradation products from the NB esters contain a nitrobenzaldehyde, which not only is toxic on its own, but also absorbs UV light and degrades further into other ill-defined products. A recent example for reducing toxicity of the products in the photo-induced reaction has been reported for the design of coumarin-bearing photocleavable polymer-anticancer drug 5-fluorouracil conjugates as prodrugs, in which the disruption of the micelles is accompanied by the release of the drug *via* UV irradiation.[147] Third, the light source used to trigger the photo-reactions of the micellar systems should be delicately selected in order to achieve their clinical therapy. As UV light apparatus with variable wavelength and intensity is cheap and easily set up in laboratory, UV-responsive polymeric micelles are well studied.[48,50,53,54,102,148-152] However, UV radiations are detrimental to the healthy tissues and their penetration into living tissues is rather limited. Compared with UV light, the absorption of NIR light (lower energy radiation with a reduced absorption and scattering by biological media and hence deeper penetration) can be implemented through a two-photon process. The general mechanism is that two-photon absorption of NIR light provides a similar light energy to activate the photoreactions of photochromic moieties as one photon absorption of UV light.[65,153,154] These features make the NIR-responsive polymeric micelles promising for on-demand drug delivery and clinical therapy.[36,38,85,107,155] Last but not least, so far as we know, a mountain of research work is focused on the single photo-reaction mechanism system, which certainly limits the functions and applications of the photo-responsive polymeric micelles. Therefore, the design of photo-responsive polymeric micelles with multi-photo-reaction mechanisms will be bound to opening a new avenue for nanocarrier and broadening the application in the field of biomedicine. With respect to these four issues, although some interesting solutions have been recently proposed, there is still much room and increasing efforts need to be made in the field for further developments.

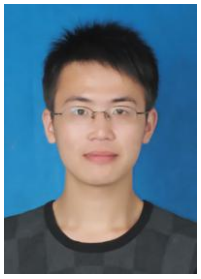
Acknowledgements

We thank the National Basic Research Program (2012CB821500, 2013CB834506) and China National Funds for Distinguished Young Scientists (21025417) for financial support.

Nomenclature

AN	Acetonitrile
ATRP	Atom transfer radical polymerization
AuNR	Au-nanorod
AZO	Azobenzene
CD	Cyclodextrin
CMC	Critical micelle concentration
CSS	Cholesterylsuccinyl silane
CTAB	Cetyltrimethylammonium bromide
Dex	Dextran
DNQ	2-Diazo-1,2-naphthoquinone
DOX	Doxorubicin
DTE	Dithienylethene
FRET	Fluorescence resonance energy transfer
3-IC	3-Indenecarboxylic acid
LC	Liquid crystal
LCST	Lower critical solution temperature
MR	Magnetic resonance
NB	*o*-Nitrobenzyl
NCCMs	Non-covalently connected micelles
NIR	Near infrared
PCMA	Poly(coumarin methacrylate)
PDT	Photodynamics therapy system
PEO	Poly(ethylene oxide)
PMA	Poly(methacrylate)
PMAA	Poly(methacrylic acid)
PMMA	Poly(methyl methacrylate)
PNIPAM	Poly(*N*-isopropylacrylamide)
PTX	Paclitaxel
SP	Spiropyran
THF	Tetrahydrofuran
UV	Ultraviolet

Curriculum Vitae



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