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ORIGINAL CONTRIBUTION

A dual stimuli-responsive amphiphilic polymer: reversible self-assembly and rate-controlled drug release

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Abstract We report the dual stimuli-responsive self-assembly and rate-controlled drug release of a novel functionalized PEG amphiphilic polymer (**FcC_{11}AzoPEG**) in aqueous solution. The novel **FcC_{11}AzoPEG** amphiphilic polymer was synthesized by the esterification reaction of poly (ethylene glycol) methyl ether (PEG) and 4-(4′-(11-ferrocenyl-undecanoxy)) azobenzoic acid. The azobenzene (Azo) and ferrocene (Fc) moieties respectively afford the polymer a slow photo-response and a fast redox-response. Upon exposure to different stimuli (light irradiation, redox reaction, and a combination of light irradiation and redox reaction), **FcC_{11}AzoPEG** in aqueous solution can reversibly self-assemble into various nanostructures and also disassemble either slowly by light irradiation or fast by redox reaction in an appropriate concentration range. Moreover, the drug release from the drug-loaded micelles can be precisely controlled by different stimuli: a slow release rate and a small amount of release for UV irradiation, a fast rate and a medium amount of release for oxidation by $Fe_2(SO_4)_3$, and a large amount of release for the combined stimulation of UV irradiation and oxidation by $Fe_2(SO_4)_3$. This work not only demonstrates the effect of stimuli-induced amphiphilicity change of functional groups on the solution aggregation behavior of functionalized PEG amphiphilic polymers but also provides a useful smart system with great potential application in drug delivery.

Keywords Multi-stimuli response · Functionalized PEG · Amphiphilic polymer · Drug release · Rate controlled

Introduction

In the past decades, amphiphilic polymers have attracted considerable attention due to their potential applications in drug and gene delivery systems [1–5]. Amphiphilic polymers in aqueous solutions can self-assemble into polymeric micelles which consist of hydrophobic cores and hydrophilic shells. As it well known, the physicochemical properties [6, 7] of amphiphilic polymers containing stimuli-responsive groups will reversibly change in response to external stimuli such as light [8], temperature [9], gas [10], redox [11], and pH [12], leading to the variation of the hydrophilic-lipophilic balance (HLB) of polymers [13], which has been used to tune the self-assembly and disassembly of stimuli-responsive amphiphilic polymers in dilute aqueous solution. When the drugs are loaded into the micellar cores of amphiphilic polymers by the hydrophobic interactions between drugs and hydrophobic cores, the drugs can be released during the progress of the disaggregation or disassembly of micelles when exposed to external stimulus [14–16].

Compared to the single stimuli-responsive polymers, multiple stimuli-responsive amphiphilic polymers containing two or more stimuli-sensitive groups have the advantages that the magnitude of amphiphilicity change of polymers can be readily controlled to a certain degree when exposed to different stimuli [17]. If drugs are encapsulated within the stimuli-responsive micelles, the drug release of encapsulated micelles will be controlled and diversified with the variation of the amphiphilicity of micelles. Hence, considerable attentions have been attracted to the multiple stimuli-responsive amphiphilic

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polymers in recent years. For example, Yu et al. [18] recently reported a dual stimuli responsive amphiphilic polymer that the disulfide cross-linked polyurethane micelle can be photo-cleaved under visible-light irradiation, shrunken to smaller nanoparticles at high pH, and swollen at low pH in aqueous solution. Also, Jie et al. [19] reported that the micelles of an amphiphilic block copolymer in water showed triple tunable responses under the stimuli of temperature, pH, and light. However, most studies focused on new stimuli and combinations of different stimuli up to now [20–22]. In view of the complexity of the illness and lesions, for drug delivery and gene delivery systems, not only the amount of the drug release needs to be controlled but also the rate of release. Namely, in some cases, the drug must be fast released, but in other cases, the persistent and slow drug release is necessary [23]. Thus, the polymeric micelles with different stimuli-responsive rates may be more suitable for the controlled drug release in realistic environments. To the best of our knowledge, the amphiphilic with controlled stimuli-responsive rate has been scarcely reported thus far [24, 25]. Recently, Zhao [25] et al. reported that the micelle of a dual stimuli-responsive polymer can be disintegrated either rapidly by UV irradiation or slowly by a reducing agent. However, this irreversible disaggregation of micelles will bring fragments into the system, which may be harmful to human health during the process of the drug delivery and gene delivery. To design a reversible self-assembly and disassembly system with controlled multiple stimuli-responsive rates is a great advantage.

In the past decades, the amphiphilic polymers containing azobenzene (Azo) and/or ferrocene (Fc) moieties had been well investigated [26, 27]. It is well known that Azo moiety can undergo slow and reversible *trans-to-cis* photo-isomerization with a small magnitude of amphiphilicity change [28]. On the other hand, hydrophobic Fc groups can be quickly oxidized (Ox) into hydrophilic ferrocenium cations (Fc^+) and then reversibly reduced (Red) by reducer [27]. In view of their different responsive rates and magnitude of amphiphilicity change, it may be interesting to design a novel amphiphilic polymer containing the above two functional groups, thereby the reversible and fast/slow rate-controlled self-assembly and disassembly of the amphiphilic polymer in aqueous solution can be realized upon exposure to different stimuli.

In this work, we described the dual stimuli-responsive self-assembly and its rate-controlled drug release behavior of a novel functionalized PEG amphiphilic polymer (**FcC_{11}AzoPEG**) containing both ferrocene and azobenzene moieties in aqueous solution. The novel functionalized PEG amphiphilic polymer was synthesized by the esterification reaction of poly (ethylene glycol) methyl ether (PEG) and the 4-(4′-(11-ferrocenyl-undecanoxy))azobenzoic acid **6** (Scheme 1). As shown in Scheme 2, the amphiphilic polymer **FcC_{11}AzoPEG** in aqueous solution can self-assemble into different sizes of micelles as the polymer concentration increases, and the micelles can be also disaggregated upon exposure to different stimuli (UV, redox, and the combined stimulation of UV and redox). Moreover, the reversible assembly and disassembly of the polymer in aqueous solution can be controlled either quickly by redox reaction or slowly by light irradiation. Such dual stimuli-responsive polymeric micelles was used as a carrier for encapsulation and release of a guest molecule (rhodamine 6G), and the release rate and amount of R6G can be precisely controlled when exposed to different stimuli.

Experimental section

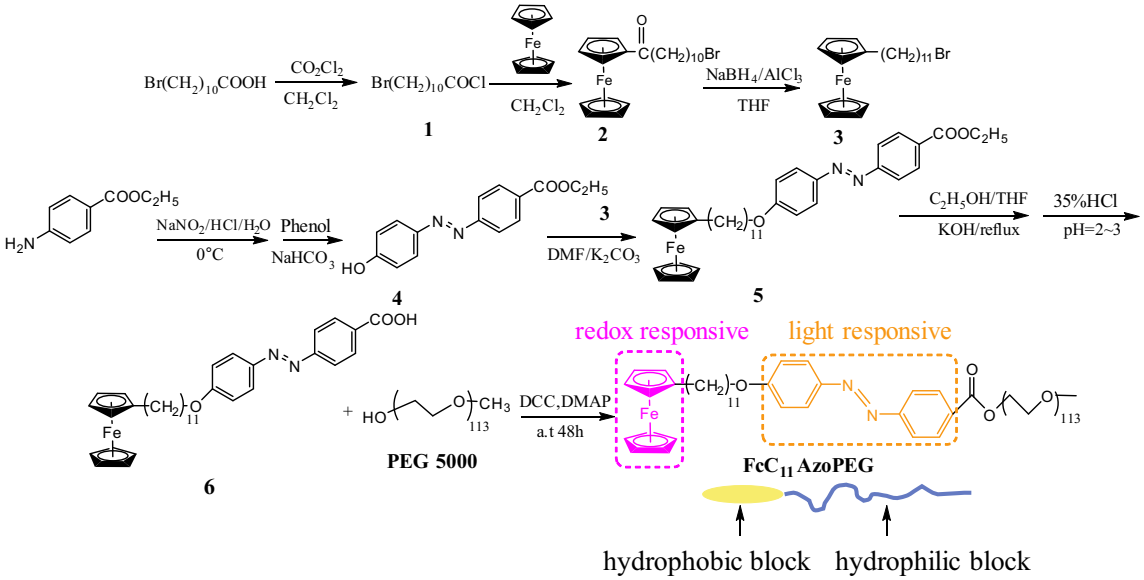
Materials

Poly (ethylene glycol) methyl ether (Adamas, average M_n = 5000), ethyl p-aminobenzoate (Aldrich, purity 98%), dicyclohexylcarbodiimide (DCC) (Aldrich, purity 98%), bromoundecanoic acid (Aldrich, purity: 98%), rhodamine 6G (Aldrich, purity: 98%), phenol (J&K Chemical, purity 99.5%), and 11-ethyl 4-aminobenzoate (DMAP) (J&K Chemical, purity 98%) were used as received. Dichloromethane (DCM), tetrahydrofuran (THF), and N,N-dimethylformamide (DMF) were dried with CaH_2 and distilled under reduced pressure prior to use. All of other chemical reagents were purified according to the standard procedures. Water used in all experiments was deionized and filtered with a Millipore purification apparatus with a resistivity of more than 18.25 MΩ cm.

Synthesis procedure

The synthesis route of **FcC_{11}AzoPEG** are shown in Scheme 1. First, the 4-(4′-(11-ferrocenyl-undecanoxy))azobenzoic acid (**6**) was synthesized according to the same procedure reported in our previous study in detail [29]. The structure of compound **6** was characterized by ^{1}H NMR and FT-IR spectra in detail (Fig. S1, ESI†).^{1}H NMR ($CDCl_3$, TMS) δ (ppm) 13.25(s_{broad}, 1H, COO*H*), 8.21 (d, 2H, Ar–*H*), 8.029 (q, 4H, Ar–*H*), 7.027 (d, 2H, Ar–*H*), 4.199 (m, 9H, *H*(Cp)), 4.029 (t, 2H, –C*H*$_2$–O–Ar), 2.61 (t, 2H, Cp–C*H*$_2$–), 1.869 (m, 2H, –CH$_2$–C*H*$_2$–O–Ar), 1.53–1.34 (m, 16H, –C*H*$_2$–Anal. Calcd for **FeC_{11}AzoCOOH**: C, 71.05; H, 7.24; N, 4.6; O, 7.90; Fe, 9.21. Found: C, 71.15; H, 7.25; N, 4.7.

Second, **FcC_{11}AzoPEG** was synthesized through the esterification of PEG and **6**. A mixture of compound **6** (0.175 g,

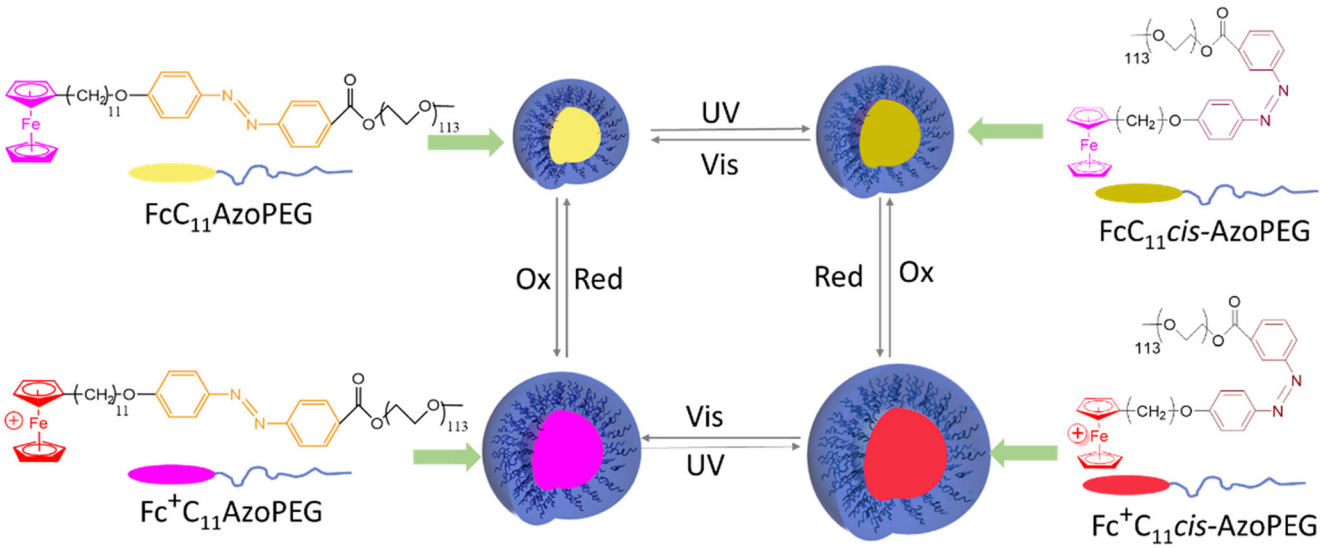


Scheme 1 Synthesis routes of **FcC_{11}AzoCOOH** and **FcC_{11}AzoPEG**

0.3 mmol), PEG5000–OCH_3 (1.25 g, 0.25 mmol), DMAP (0.0244 g, 0.2 mmol), and DCC (0.1917 g, 1 mmol) was dissolved in 20 mL dry DCM, and then added the dissolved mixture in a round-bottomed flask with a magneton and stirred at 25 °C. After about 48 h, the reaction endpoint was determined by thin layer chromatography (TLC) analysis. The solution was evaporated in vacuum, and the residue was purified by flash column chromatography on silica gel and vacuum-dried. Then, the solid polymer was dissolved in 10 mL water. Finally, the mixture was purified via exhaustive dialysis (molecular weight cut-off (MWCO) = 2000 Da) against purified water and vacuum-dried to yield a yellow solid polymer (1.25 g, 87%). The purified polymer was characterized in detail by GPC (Fig. S2B, ESI†), ^{1}H NMR, and FTIR spectra. The M_n determined by GPC is 5700 (theoretical value: 5564), and the polydispersity index (PDI) is 1.1. ^{1}H NMR spectrum is shown in Fig. 1. ^{1}H NMR ($CDCl_3$, TMS) δ (ppm) 8.19 (d, 2H, Ar–*H*), 7.92 (q, 4H, Ar–*H*), 7.03 (d, 2H, Ar–*H*), 4.51 (t, 2H, Ar–COO–C*H*$_2$–), 4.23 (m, 9H, *H*(Cp)), 4.07 (t, 2H, –C*H*$_2$–O–Ar), 3.87 (t, 2H, Ar–COO–CH_2–C*H*$_2$–), 3.67 (m, 532H,Ar–COO–CH_2–CH_2–O–CH_2–C*H*$_2$), 3.39 (s, 3H, –O–C*H*$_3$), 2.23 (t, 2H, Cp–C*H*$_2$–), 1.50 (m, 2H,–C*H*$_2$–CH_2–O–Ar), 1.45–1.29 (m, 16H, –C*H*$_2$). FT-IR of the polymer is given in Fig. S2A (ESI†).

Instruments

^{1}H NMR spectra were recorded on a Bruker Avance 400 (400 MHz) spectrometer. The size distribution of the micelles was analyzed at 25 °C by dynamic light scattering



Scheme 2 The micellar transition of **FcC_{11}AzoPEG** solution upon exposure to different stimuli

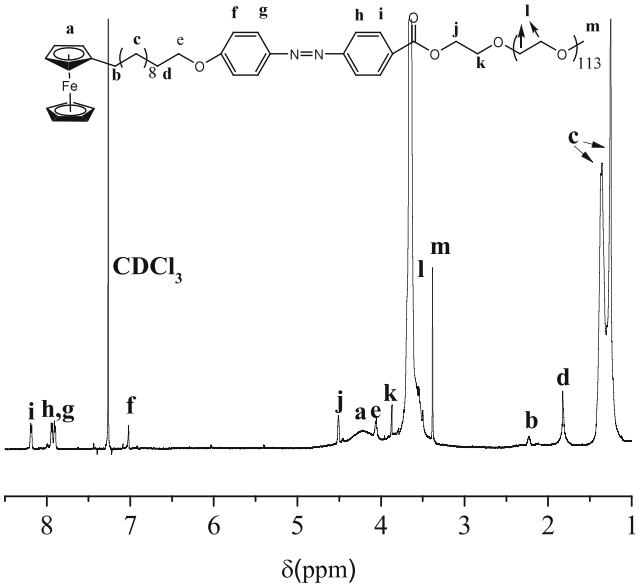


Fig. 1 ^{1}H NMR spectrum of **FcC$_{11}$AzoPEG** measured in $CDCl_3$

(DLS), a Malvern Nano-ZS 90 Zetasizer using a monochromatic coherent He–Ne laser (633 nm) as the light source, and a detector that detected the scattered light at an angle of 90°. Molecular weights and molecular weight distributions of polymers were measured by gel permeation chromatography (GPC) with a Waters 515 pump/M717 data module/R410 differential refractometer using THF as the flow phase with a flow rate of 1.5 mL min^{-1}, monodisperse PEO as a standard, and a column temperature of 40 °C. UV–vis absorption spectra were determined on a Hitachi U-3010 UV–vis spectrophotometer. Transmission electron microscopy (TEM) images were obtained from a JEM-2100HR microscope with an acceleration voltage of 200 kV, and samples were taken through the homemade atomizer to aerospray cellulose-coated copper grids and then stained with 2 wt.% uranyl acetate before observation. Surface tensions were obtained from a surface tension meter (Dataphysics OCA20, Germany) at 25 °C. Fourier transform infrared (FTIR) spectra were obtained on a Thermo Nicolet 6700 spectrometer using KBr substrates.

Preparation of samples

Preparation of micellar aggregates

One hundred milligrams of amphiphilic polymer was dissolved in 10 mL of deionized water for a night to obtain 10 g/L polymer solution for further experiments.

Stimuli-response of polymer

The *cis*-form **FcC$_{11}$*cis*-AzoPEG** solution was prepared after irradiation by a UV light with a wavelength of 365 nm (15 W). To recover the *trans*-form of the polymer, the **FcC$_{11}$*cis*-AzoPEG** solution was irradiated by a visible light (green light, λ = 577–492 nm, 22 W). The oxidation state **Fc^{+}C$_{11}$AzoPEG** solution was prepared with 0.52 equiv. $Fe_2(SO_4)_3$ corresponding to the total ferrocene units in polymer and stirred until the yellow color turned to blue. To reduce the oxidized polymers, 0.55 equiv. vitamin C (Vc) was added to the **Fc^{+}C$_{11}$AzoPEG** solution and stirred several seconds until the blue color completely recovered to yellow.

Loading and release of R6G

To prepare R6G-loaded micelles, 100 mg of polymer and 5 mg of R6G were dissolved in 1 mL DMF and slowly dropped into 10 mL of deionized water, then stirred at room temperature for 12 h. The solution was purified via exhaustive dialysis (molecular weight cut-off (MWCO) = 2000 Da) against deionized water for 3 days to remove the remaining DMF and an excess of R6G until the water outside the dialysis tube exhibited negligible R6G. The final concentration of polymer packed with R6G was 5.0 g/L. The rate of drug release was determined as follows: 2.0 mL of drug-loaded micellar was exposed to different stimuli to release drugs in solution. To confirm the amount of released drugs, the solution was transferred into a dialysis tube (MWCO = 2000 Da) against deionized water. Two milliliters of release media was taken out at desired interval and measured by UV–vis spectroscopy. The amount of released drug can be obtained when the absorption at 527 nm remained unchanged.

Results and discussion

Reversible stimuli-responsive behavior of polymer in solution

In order to confirm the reversible photo/redox responsive behavior of the polymer, the UV–vis spectroscopy of polymer solution was performed. Figure 2a shows the UV–vis spectra of 1.0 g/L **FcC$_{11}$AzoPEG** aqueous solution exposed to 365 nm light for different time. The initial solution shows a characteristic peak at 355 nm and a small peak at 450 nm. With increasing exposure, the peak at 355 nm reduces gradually due to π to π^* transition of azobenzene. Meanwhile, the intensity of peak at 450 nm increases slightly due to the n to π^* transition, indicating that Azo groups photo-isomerize from *trans*-to-*cis* form [30]. After being exposed to UV light for 180 s (3 min), the UV–vis spectra remain invariable, indicating the solution have reached the *cis*-stationary state. Immediately, the **FcC$_{11}$*cis*-AzoPEG** solution was exposed to visible light. As shown in Fig. 2b, the peak intensity at 355 nm gradually

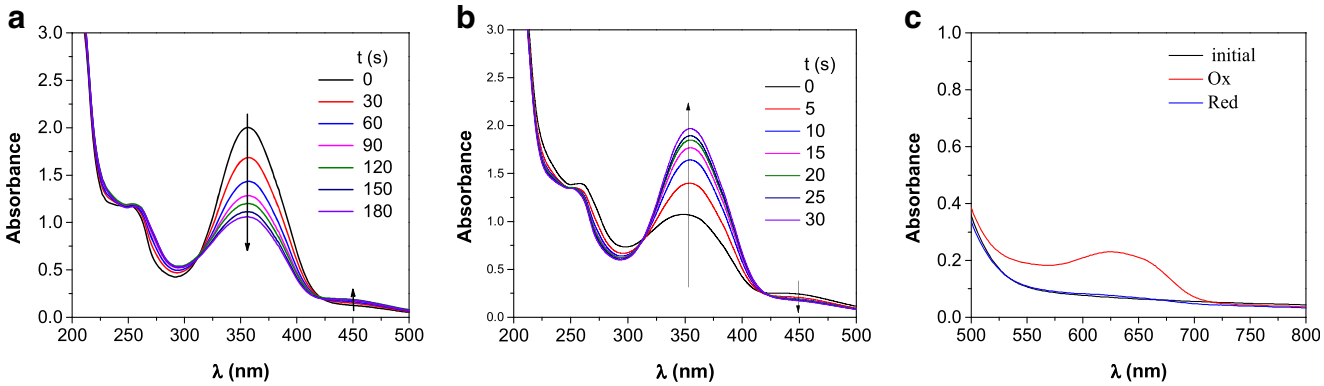


Fig. 2 The UV–vis spectra of 1 g/L **FcC$_{11}$AzoPEG** aqueous solutions: **a** after UV light irradiation for different time, **b** after visible light irradiation for different time, **c** after oxidization by $Fe_2(SO_4)_3$ and reduction by vitamin C

increases as time progresses and recovers its initial intensity after irradiation for 30 s, indicative of a completely reversible *cis*-trans conversion [31]. And then, the reversible redox reaction of Fc groups was also studied by UV–vis measurements. From Fig. 2c with the addition of $Fe_2(SO_4)_3$ and stirring for a few seconds, the UV–vis spectroscopy shows an obvious absorption peak at 630 nm, corresponding to the Fc^+ groups [32]. Subsequently, after the addition of the reductant (vitamin C) into the oxidation state solution, the absorption at 630 nm disappears, confirming a rapid and reversible redox stimuli-responsive behavior of **FcC$_{11}$AzoPEG** in aqueous solution. The results indicate that the polymer exhibits a reversible light/redox-responsive behavior. And, the reversible stimuli-responsive behavior can be realized either slowly by light irradiation or quickly by the redox reaction.

Critical aggregation concentration (*CAC*) of polymer in aqueous solution

As discussed above, the *trans-cis* conversion of Azo and the Fc-Fc^+ conversion will lead to a reversible change of amphiphilicity of polymer, thereby changing the self-assembled nanostructure of amphiphilic polymer in aqueous solution [28, 33]. Hence, surface tension measurements were carried out for **FcC$_{11}$AzoPEG** aqueous solution to validate the change in the HLB of the polymer upon exposure to different stimuli at 25 °C, as shown in Fig. 3a. When the

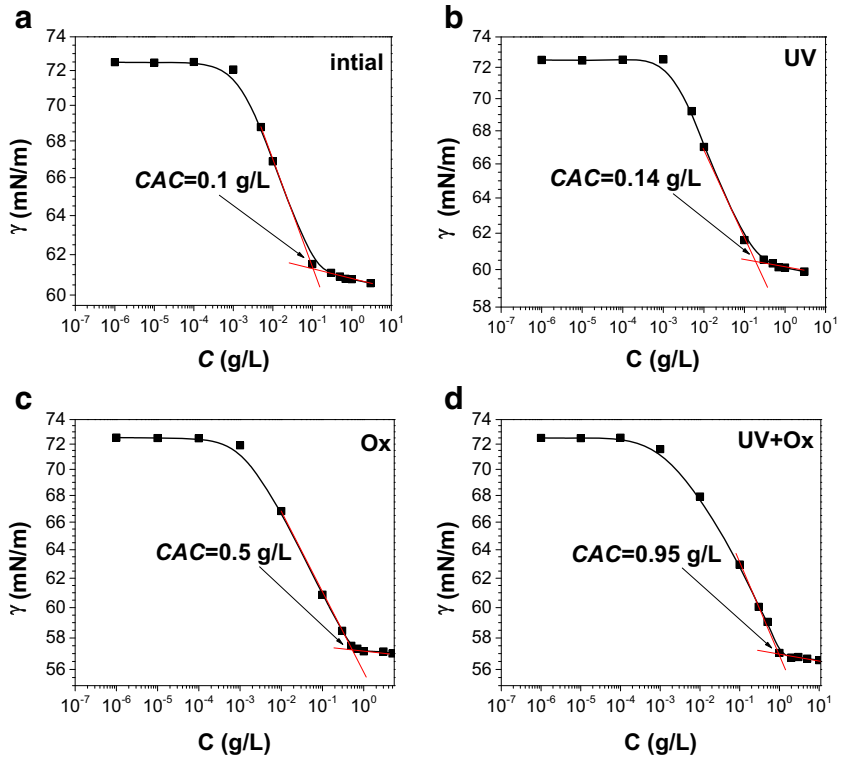


Fig. 3 Plots of surface tensions (γ) against the concentration (C) of **FcC$_{11}$AzoPEG** aqueous solution upon exposure to different stimuli

Table 1 The *CAC* values of polymer in aqueous solution upon exposure to different stimuli

	initial	UV	oxidation	UV + oxidation
structure	FcC_{11}AzoPEG	FcC_{11}*cis*-AzoPEG	$Fc^{+}C_{11}$AzoPEG	$Fc^{+}C_{11}$*cis*-AzoPEG
CAC (g/L)	0.1	0.14	0.5	0.95

concentrations are below 10^{-4} g/L, the surface tension of polymer solutions is nearly the same as deionized water. With the concentration increases, the surface tension decreases sharply, and then remains at a constant value. The determined *CAC* values are 0.1 g/L (Fig. 3a) and 0.14 g/L (Fig. 3b) for **FcC_{11}*trans*-AzoPEG** and **FcC_{11}*cis*-AzoPEG**, respectively. The results indicate that the light irradiation has a slight influence on *CAC* because the variation of the dipole moment caused by the *trans*-to-*cis* isomerization of Azo group is relatively small [28]. With the oxidation of Fc group by $Fe_2(SO_4)_3$, the *CAC* value of the oxidation state **$Fc^{+}C_{11}$AzoPEG** solution increases to 0.5 g/L because of the enhanced hydrophilicity of Fc^{+} cation (Fig. 3c), which is consistent with ferrocenyl surfactant [27]. Furthermore, after being exposed to UV irradiation and oxidation agent simultaneously, the *cis*-form oxidation state **$Fc^{+}C_{11}$*cis*-AzoPEG** solution significantly increases its *CAC* value from the initial 0.1 to 0.95 g/L (Fig. 3d). For an easy comparison, the *CAC* values are listed in Table 1 for **FcC_{11}AzoPEG** after being exposed to different stimuli. It is therefore clear that the *CAC* values gradually increase as follows: $CAC_{initial} < CAC_{UV} < CAC_{Ox} < CAC_{UV+Ox.}$ This means that the HLB values of those polymers increase in the same order: **FcC_{11}AzoPEG** < **FcC_{11}*cis*-AzoPEG** < **$Fc^{+}C_{11}$AzoPEG** < **$Fc^{+}C_{11}$*cis*-AzoPEG**. This suggests that the self-assembly and disassembly of polymer can be reversibly controlled by applying different stimuli at different concentrations with the variation of the *CAC* values of polymer while being exposed to different stimuli [34].

Reversible self-assembly and disassembly of polymer

It has been well established that the aggregation morphology of polymers in aqueous solution depends on their HLB [35]. Hence, TEM and DLS were performed to study the aggregation morphology of **FcC_{11}AzoPEG** while being exposed to different stimuli. First, its photo-responsive aggregation behavior in aqueous solution was studied. Theoretically, the UV irradiation will lead to the dissociation of micelles when the polymer concentration (*C*) is between 0.1 and 0.14 g/L, and the transition of micelles will occur by UV light irradiation when *C* is above 0.14 g/L. Therefore, taking into consideration the measuring tolerance, we just studied the aggregation morphology of polymer solution for $C > 0.14$ g/L (0.3 g/L). Micelles with diameter of about 15–25 nm are observed in the **FcC_{11}AzoPEG** aqueous solution, as shown in Fig. 4a(a). While being exposed to UV irradiation for 3 min, the micelles slowly turn into larger micelles with diameter of about 25–35 nm (Fig. 4a(b)). As expected, while being exposed to visible light for 30 s, the micelles reversibly recover their initial sizes. The driving force of the size expansion may be the slightly enhanced hydrophilicity of **FcC_{11}*cis*-AzoPEG** solution upon exposure to UV light. Therefore, the formation of *cis*-form micelles needs a slight greater aggregation number, which will lead to the expansion of micelles. Meanwhile, the hydrodynamic diameter (D_h) of polymer was determined by DLS, which also exhibits similar results. As shown in Fig. 4c, D_h is 25 nm without stimulus, and then the D_h value increases to 48 nm after UV light irradiation. Taking into account the

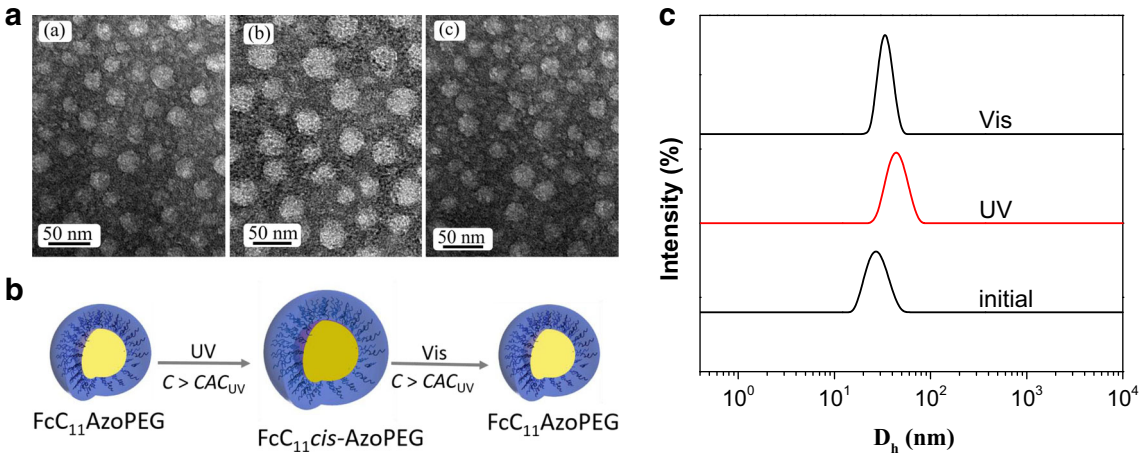


Fig. 4 TEM images of the micelles **a** (*a*) initial micelles, (*b*) after UV light irradiation for 3 min, (*c*) after visible light irradiation for 30 s. **b** Schematic illustration of reversible structural changes of micelles under UV/visible light. **c** The size of micelles obtained from DLS in 0.3 g/L aqueous solution upon exposure to different stimuli

degree of hydration, it is normal that the D_h determined by DLS is a little larger than the mean diameter determined by TEM [36].

Then, the redox-responsive reversible self-assembly of polymer was also studied by TEM and DLS. Figure 5a shows the TEM images of micellar assemblies of 0.3 g/L **FcC_{11}AzoPEG** solution, where C is between its $CAC_{initial}$ and CAC_{Ox}, and micelles with the diameter of 15–25 nm are observed too (Fig. 5a(a)). Interestingly, with the addition of $Fe_2(SO_4)_3$ for a few seconds, the micelles are totally disassembled (Fig. 5a(b)) and reversibly recover after reduction by Vc (Fig. 5a(c)) immediately. What is more, when C increases from 0.3 to 0.7 g/L, which is above its CAC_{Ox}, the diameter of micelles increases from 15 to 25 nm (Fig. 5a(d)) to 45–50 nm (Fig. 5a(e)) after the micelles were oxidized by $Fe_2(SO_4)_3$. As expected, these micelles reversibly recover their initial sizes after reduction by Vc (Fig. 5a(f)). Except for the enhancement of hydrophilicity of Fc^+ groups, the electrostatic repulsion between the Fc^+ groups will also contribute to the expansion of micelles [37]. The results were further confirmed by DLS (Fig. S3 A, ESI†).

Furthermore, we investigated the stimuli-responsive behavior of the polymer when UV light and $Fe_2(SO_4)_3$ were input simultaneously. The micelles with diameter of 45–50 nm are observed after oxidation when C (0.7 g/L) is between the CAC_{ox} and CAC_{UV+ox} (Fig. 6a(a)). Analogously, the micelles are totally disassembled (Fig. 6a(b)) after UV irradiation and oxidation and reversibly recover after visible irradiation and reduction by Vc (Fig. 6a(c)). It is worth noting that when C (1 g/L) is above its CAC_{UV+ox}, after the polymer solution is exposed to both UV irradiation and oxidation, the diameter of micelles increase to 85–95 nm as shown in

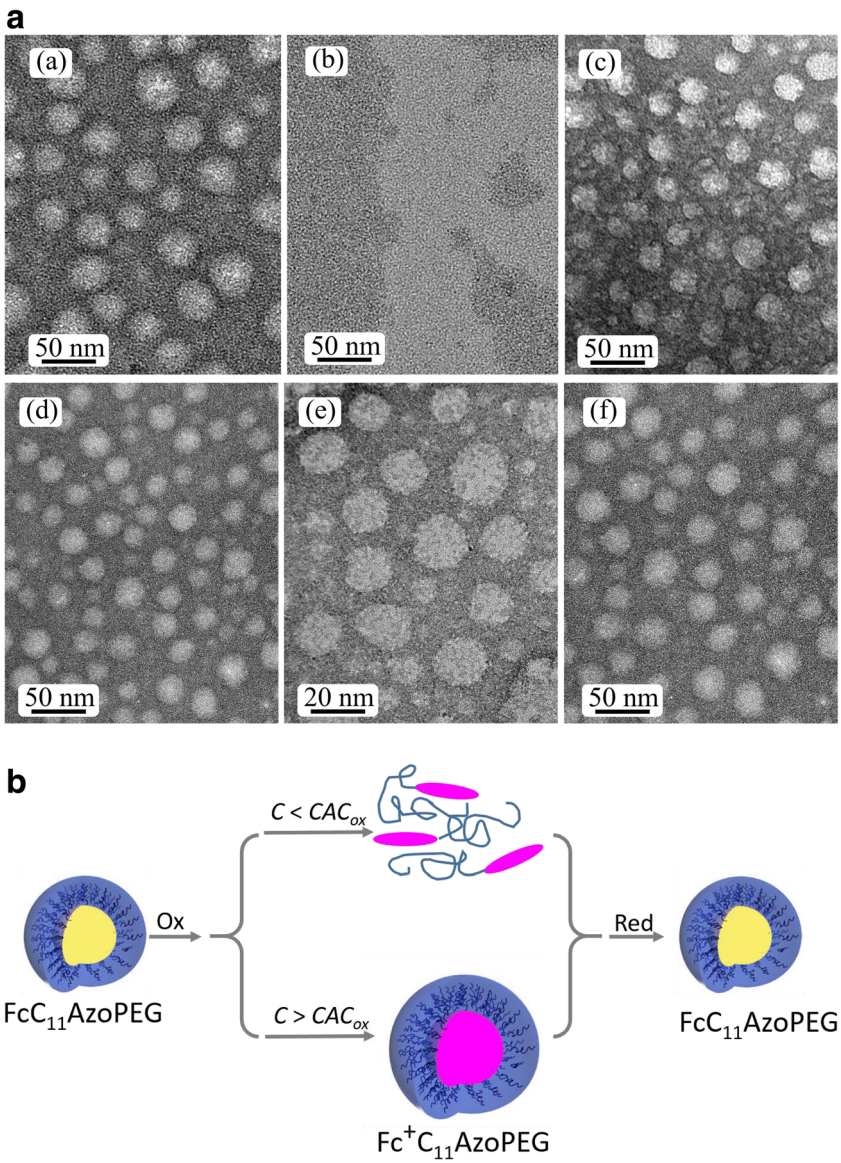


Fig. 5 TEM images of micelles **a** (*a*) initial micelles; (*b*) after oxidation by $Fe_2(SO_4)_3$, (*c*) after reduction by Vc in 0.3 g/L aqueous solution, (*d*) initial micelles, (*e*) after oxidation by $Fe_2(SO_4)_3$ and (*f*) after reduction by Vc in 0.7 g/L aqueous solutions. **b** Schematic illustration of the reversible micellar transition by redox

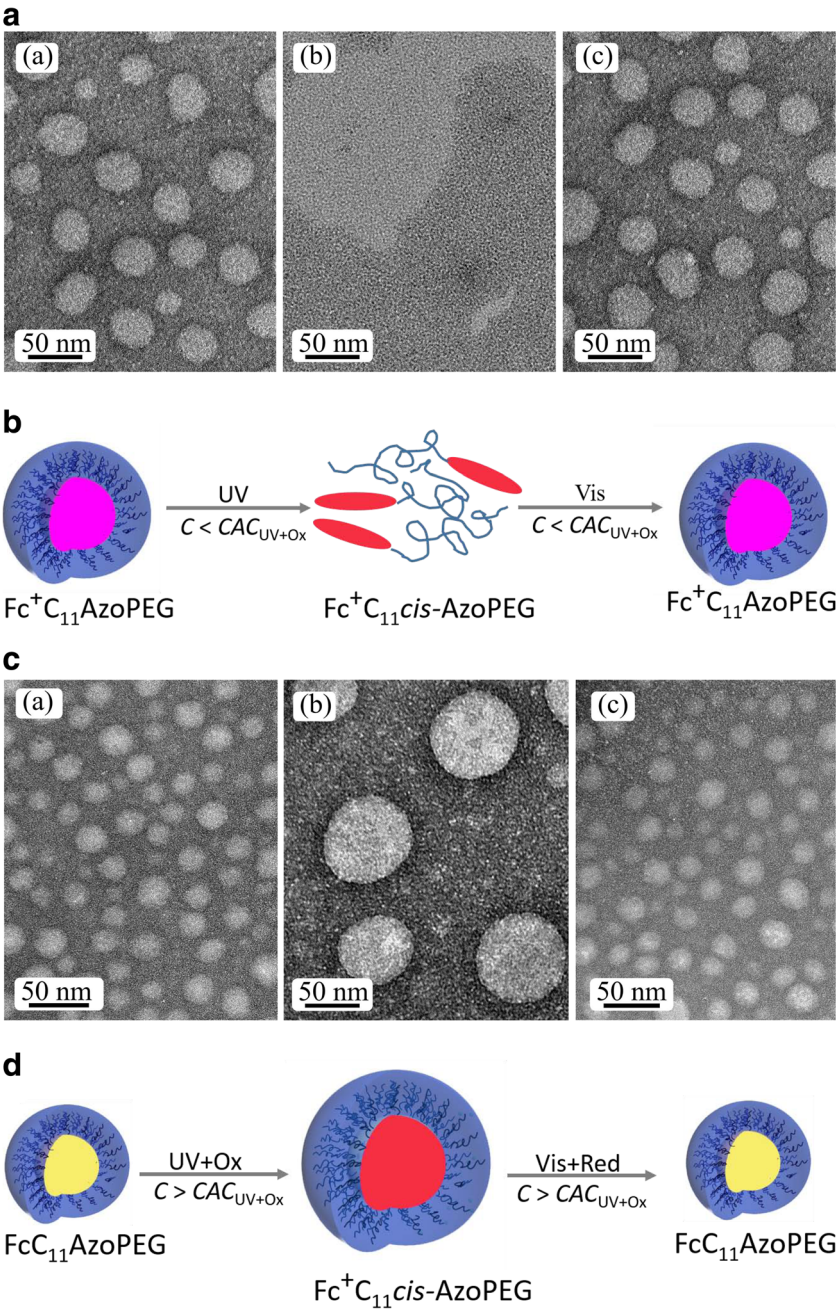


Fig. 6 TEM images of micelles **a** (*a*) after oxidation by $Fe_2(SO_4)_3$, (*b*) after oxidation by $Fe_2(SO_4)_3$ and UV light irradiation, (*c*) after visible light irradiation. **b** Schematic illustration of the reversible structural changes of micelles by redox or UV in 0.7 g/L aqueous solution. TEM images of micelles **c** (*a*) initial micelles, (*b*) after oxidation by $Fe_2(SO_4)_3$ and UV light irradiation, (*c*) after reduction by Vc and visible light irradiation. **d** Schematic illustration of the reversible structural change of micelles by redox and UV in 1 g/L aqueous solution

Fig. 6c(b), resulting from remarkable synergistic effects of the *trans*-to-*cis* photo-isomerization of Azo groups and the reduction-oxidation state transition of Fc groups. On the one hand, the hydrophilicity of polymer will be remarkable enhanced by the synergistic effect of the *cis*-Azo and Fc^+, leading to the swelling of micelles. On the other hand, the electrostatic repulsion between the Fc^+ groups will also contribute to the expansion of micelles. As expected, after being exposed to visible light and reducing agent, the micelles recover their initial states immediately (Fig. 6c(c)). Those phenomenon are consistent with the DLS results (Fig. S3 B, ESI†).

Controlled release of R6G from polymer micelles

As aforementioned, the **FcC_{11}AzoPEG** polymer exhibits rate-controllable self-assembly and disassembly behavior in response to light irradiation or redox reaction. It has been well studied that the drug molecule can be capsulated into the micellar cores of amphiphilic polymer, then the controlled release of drug can be realized with the disassembly or disaggregation of micelles [38, 39]. Here, the controlled release of a model molecule, rhodamine 6G (**R6G**), from the **FcC_{11}AzoPEG** micellar nanoparticles was investigated by monitoring the change in absorbance of R6G at 527 nm,

because the UV–vis absorption intensity of **R6G** at 527 nm in water was proportional to its concentration (Fig. S5, ESI†). The release of **R6G** was detected by UV–vis measurements after being exposed to external stimuli for different time. The release rate was calculated according to

$$R_i = V_i C_i \Big/ V_o C_o \quad (1)$$

where V_i and C_i refer to the volumes and **R6G** concentration of the solution outside the dialysis tube, and V_0 and C_0 express the volume and concentration of **R6G**-loaded polymer inside the dialysis tube.

Figure 7 shows the drug-release curves of the **R6G**-loaded 5.0 g/L polymer when exposed to different stimuli. It can found that only less than 5% of **R6G** is released from the micelles within 10 h in the initial state without any stimuli, exhibiting favorable storage properties. Because of the strong hydrophobic interaction between **R6G** and

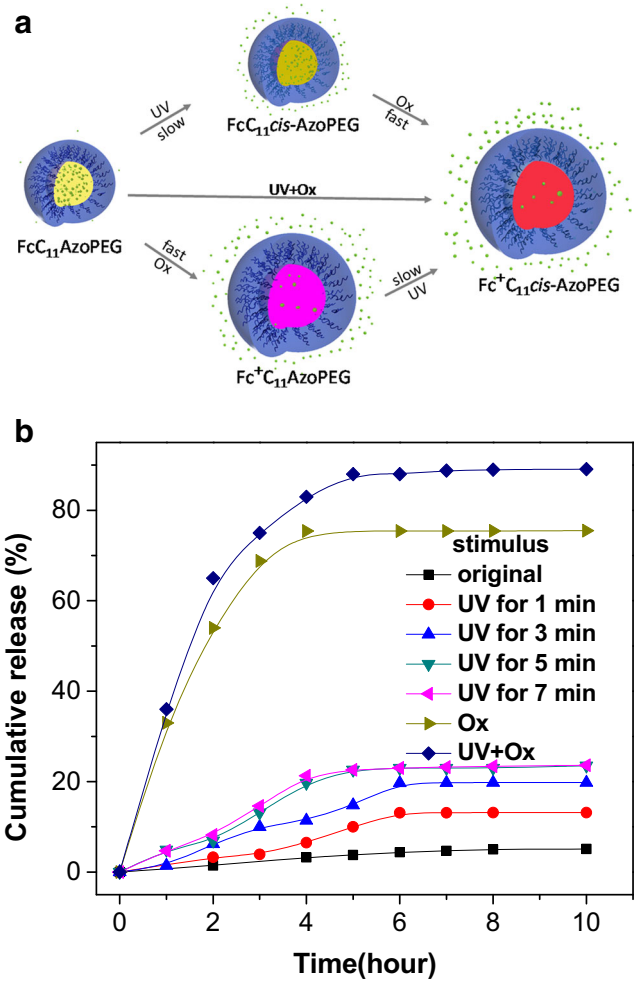


Fig. 7 **a** Illustration of the drug release under different conditions. **b** Controlled release of **R6G**-loaded 5.0 g/L polymer solution after UV irradiation for different time, oxidation by $Fe_2(SO_4)_3$, and a combined stimulation of UV and oxidation

FcC_{11}AzoPEG chains, the majority of **R6G** can be retained in the micelles [40]. Furthermore, the amount of released **R6G** will increase with increasing exposure to UV light. After UV irradiation for 1, 3, 5, and 7 min, the corresponding amount of cumulative release of drugs are 13.15, 19.7, 23.5, and 23.5%, respectively. After UV irradiation for 5 min, the amount of the released **R6G** remains unchanged. This phenomenon can be attributed to the slightly enhanced hydrophilicity of polymer induced by the slow *trans*-to-*cis* isomerization of Azo group. Subsequently, we studied that the release of **R6G** after the polymer solution was oxidized by 0.4 g/L $Fe_2(SO_4)_3$ for few seconds. From the curve, about 75% **R6G** is released eventually. This phenomenon should be contributed to the great enhanced hydrophilicity of **Fc^+C_{11}AzoPEG** caused by the fast oxidation of Fc into Fc^+, which greatly decreases the hydrophobic interactions between the drug and the core of micelle. Interestingly, a combined stimulation of UV irradiation and oxidation by $Fe_2(SO_4)_3$ will induce about 87% of **R6G** to be released eventually, indicating a sharply increased amount of drug release. This phenomenon may be caused by the fast micellar transitions and the tremendous increase of hydrophilicity of **Fc^+C_{11}cis-AzoPEG** micellar cores. Thus, the amount and rate of the drug release from the encapsulated-polymer can be readily controlled by different stimuli. A small amount of release and a slow drug release rate can be obtained by UV light irradiation, and a medium amount of release and a fast release rate can be realized by the oxidation, and a large amount of drug release can be achieved by the combined stimulation of UV light irradiation and oxidation reaction. The above results may provide us with a unique method to precisely control the drug release and satisfy different demand of drug release when exposed to different stimuli.

Conclusion

In summary, we successfully synthesized a dual stimuli-responsive functionalized PEG amphiphilic polymer **FcC_{11}AzoPEG** containing both Azo and Fc moieties. **FcC_{11}AzoPEG** in aqueous solution can reversibly self-assemble into various nanostructures and also disassemble either slowly by light irradiation or fast by redox reaction in an appropriate concentration range because of the stimuli-induced amphilicity change. In view of the magnitude of amphilicity change and stimuli-responsive rate of polymer upon exposure to different stimuli, the rate and amount of drug release from **R6G**-loaded polymeric micelles could be efficiently adjusted by different stimuli. The results are therefore of interest not only for the fabrication of multiple stimuli-responsive macromolecular self-assembly but also for the development of polymeric nano-carriers for drug release.

Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest.

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