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Consecutive Morphological Transitions in Nanoaggregates Assembled from Amphiphilic Random Copolymer via Water-Driven Micellization and Light-Triggered Dissociation

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The past decade of research has witnessed a significant progress in macromolecular self-assemblies, which offer a rich variety of morphologies and transitions.[1] Recently, potential applications in controlled drug encapsulation, circulation, and targeted release[2] have boosted new interests in the development of responsive polymer assemblies that could continuously change their morphologies in water,[3] in response to an external stimulus, such as pH[4] and temperature.[5] Most of the effort, however, has focused on the design of block copolymers with well-defined architectures and narrow polydispersity, which are often found synthetically challenging. In comparison, random copolymers with a wide range of chemical functionalities and compositions are readily available. Nevertheless, because of their ill-defined structures and broad polydispersity, little has been exploited of their assemblies in aqueous solution. Therefore, it will be intriguing to see whether it is possible to form well-ordered nanoassemblies from an amphiphilic random copolymer solution, which can undergo continuous morphological transitions. Moreover, once the desired nanoassembly is formed, it will be interesting to trigger its dissociation by an external stimulus for controlled release of encapsulants. Among various external stimuli, including pH, temperature, and ionic strength, light potentially offers better spatial and temporal control[6,7] such that the time and the site of release will be determined by when and where the irradiation light is applied.

Herein, we report a study of continuous morphological transitions from spherical micelles, through hollow tubes and wormlike rods, to large vesicles in nanoaggregates self-assembled from photoresponsive amphiphilic random copolymer, DNQMA−HEMA (Scheme 1). Through esterification of the side chain hydroxyl groups, the hydrophilic poly(hydroxyethyl methacrylate) (PHEMA) backbone is partially and randomly modified by the hydrophobic, light-responsive 2-diazo-1,2-naphthoquinone (DNQ) molecules. The micellization and transition are then triggered simply by adding water into the copolymer/DMF solution. Upon irradiation to UV light at 405 nm, large vesicles become increasingly hydrophilic with time and gradually dissociate into globular hydrogel particles in the aqueous solution (Scheme 1), releasing the encapsulated dye molecules.

As shown in Figure 1a, upon exposure to UV light, hydrophobic DNQ undergoes the Wolff rearrangement to 3-indenecarboxylate (IC), thus dramatically increasing its hydrophilicity.[8] On the basis of this photochemical reaction, we incorporated DNQ molecules to the hydrophilic PHEMA side chains (Figure 1b). The resulting DNQ-modified photoresponsive amphiphilic random copolymer has $M_w = 3.1 \times 10^5$ g mol^{-1} and polydispersity (PDI) of ~1.5 after three times dissolution−precipitation cycles. The average number of DNQ molecules attached to PHEMA side chains was estimated as ~25 mol % by ^{1}H NMR. Detailed synthesis and characterization about the random copolymer can be found in the Supporting Information (Figure S1−Figure S4). To investigate the nature of the DNQ attachment, randomly or blocky, we performed DSC study and attempted homopolymerization from DNQ functionalized HEMA monomers. A single glass transition at 36.9 °C was observed (Figure S3), which was lower than the T_g of PHEMA, 51.1 °C, suggesting that the DNQ moieties are randomly attached to the PHEMA side chains rather than formed a segregated block which is bound to have two distinctive transitions. In addition, we also found no homopolymerization from DNQ functionalized HEMA monomer via free radical

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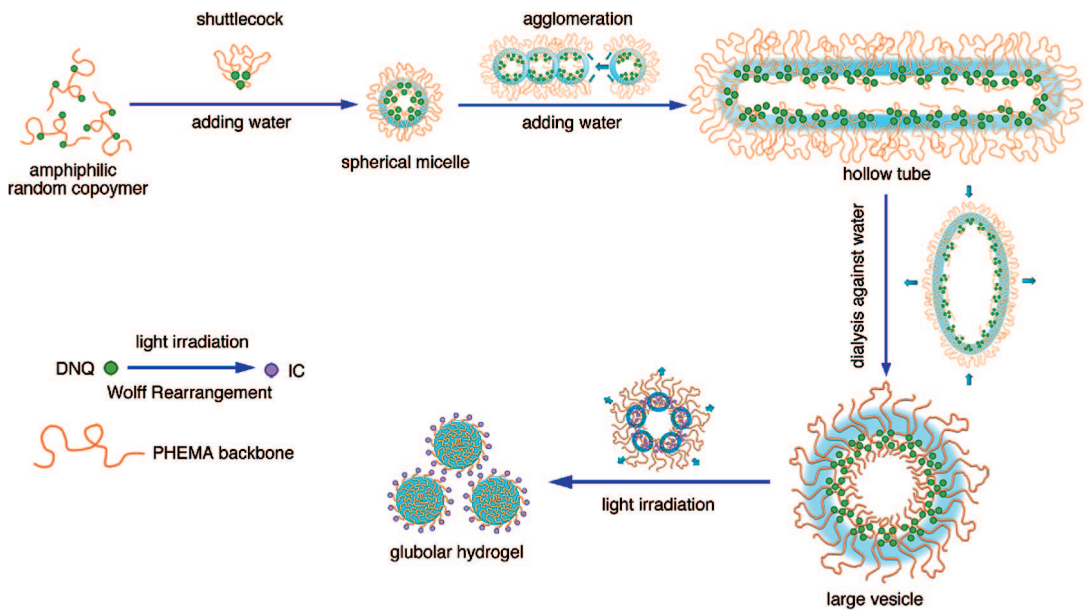
Scheme 1. Schematic Illustration of the Consecutive Morphological Transitions in Nanoaggregates Self-Assembled from Photoresponsive Amphiphilic Random Copolymer via Water-Driven Micellization and Light-Triggered Dissociation



polymerization in bulk or in solution due to the steric effect of DNQ group.

It is known that the morphology of soft assemblies from block copolymers is mainly determined by the effective interaction parameter, block length, and the ratio of different blocks.[9] Using the water-induced micellization method,[10] we first dissolved DNQMA−HEMA in DMF, a good solvent for both PHEMA and DNQ moiety, followed by addition of water, a precipitant for DNQ moiety. Below the critical water content (CWC) (18 wt %, see Figure S5),[11] the addition of water was not sufficient to induce precipitation of polymeric chains, and no aggregation was observed. When the water content was increased to 20 wt %, above CWC, the hydrophobic DNQ chains began to collapse out of water, whereas PHEMA chains maintained soluble in both DMF and H_2O. Because of the weak hydrophilicity of PHEMA backbone, we believe that in a dilute solution (10 mg mL^{-1}) the amphiphilic polymer chains first formed a "shuttlecock" morphology with a corklike hydrophobic head and a cone-shaped hydrophilic tail. To reach a stable state, several "shuttlecocks" assembled to generate spherical micelles with diameter ~35 nm (Figure 2a, 20%). When the water content further increased to 35 wt %, spherical assemblies could no longer sustain the unfavorable contact between hydrophobic core and water. To further reduce the interfacial energy between the random copolymers and water, a hollow tube, a more stable morphology, evolves, wherein the spherical micelles might agglomerate sequentially one by one through the rearrangement of the original shuttlecock-like particles (see Scheme 1, step 2). As shown in Figure 2a 35%, there are many dark regions corresponding to the relatively compact alignment of the hydrophobic domains, "shuttlecocks", along with the wall of the tubes. The diameter of the hollow tubes was found nearly identical to that of the spherical micelles, further supporting the proposed transition from the spherical micelles to hollow tubes. At higher water content of 60 wt %, wormlike rods (Figure 2a, 60%) with larger diameter (~50 nm) and shorter length (~ 300 nm) were observed as a result of the increasing inferiority of the internal environment of the assemblies. After dialysis to completely remove DMF, the nanoassemblies experienced conformational adjustment from wormlike rods to large vesicles (diameter ~ 200 nm, Figure 2a, 100%) by expanding the core while simultaneously decreasing the average surface area per hydrophilic component (A_h).[12] On one hand, the smaller the A_h, the stronger the repulsion among hydrophilic corona chains, the bigger the size and number of end-caps of the rods, at which repulsion between corona chains is lower than that in the body. On the other hand, the increasing stretching of the core leads to a rise of the diameter of the rods.

Consecutive morphological transitions might not be common in synthetic random copolymers; however, it is familiar in nature that proteins with both random sequenced hydrophilic and hydrophobic amino acids in the linear chain often associate to form stable complex morphologies.[13] In addition, the relatively high molecular weight of DNQMA−HEMA and the suitable hydrophilicity of polymer backbone also contribute to the consecutive morphological transitions. Compared with the typical molecular weight (several tens of thousands g mol^{-1}) of normal block copolymer used in self-assembly, DNQMA−HEMA has higher molecular weight (3.1×10^5 g mol^{-1}), which means the longer chain can regulate its confirmation. Furthermore, although PHEMA is often considered hydrophilic, it becomes insoluble in water when the number of repeating unit exceeds 100. This comparatively weak hydrophilicity of polymer backbone also enhances the possibility that hydrophilic chain could adjust conformation according to the movement of hydrophobic domains. With combination of the above factors,

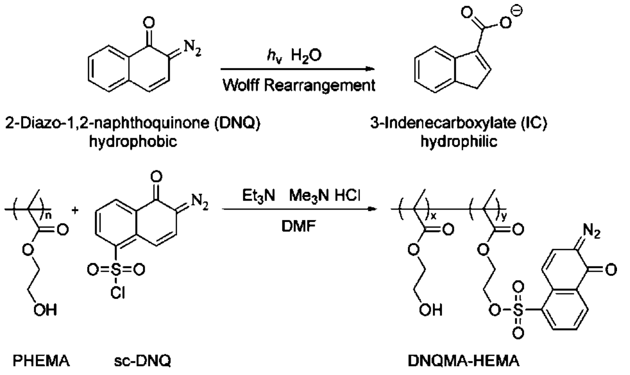


Figure 1. (a) Wolff rearrangement of DNQ under light. (b) Modification of PHEMA with sc-DNQ.

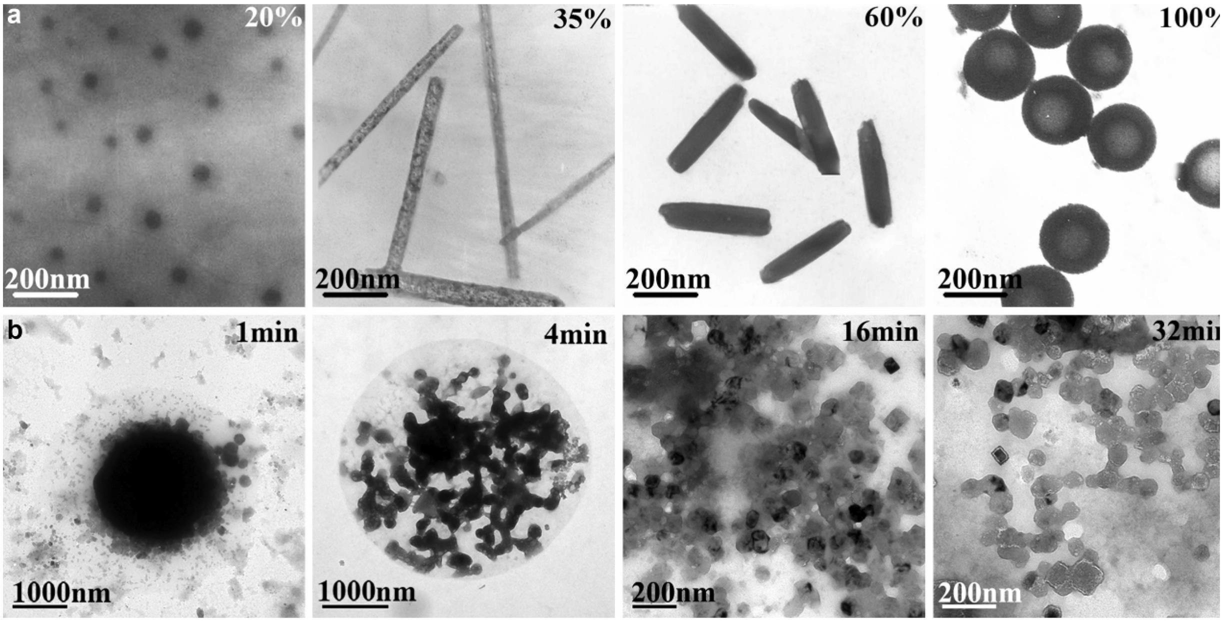


Figure 2. TEM images of nanoaggregates self-assembled from DNQMA−HEMA in DMF/H_2O solution. (a) Morphological transitions from spherical micelles, through hollow tubes and wormlike rods, to large vesicles with the increase of water content: 20, 35, 60, and 100 wt % after dialysis (from left to right). The initial polymer concentration in DMF is 10 mg mL^{-1}. (b) Light-triggered dissociation of a large vesicle in aqueous solution at different irradiation time form left to right: 1, 4, 16, and 32 min.

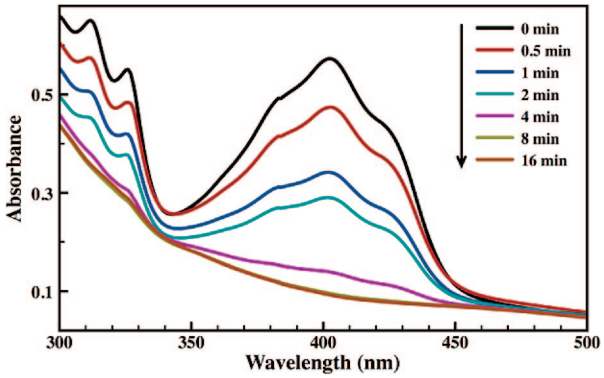


Figure 3. Time-resolved UV−vis spectra of DNQMA−HEMA in DMF solution (10 mg mL^{-1}). $\lambda = 405$ nm, power of 25 mW. Spectrum at 8 min is overlapped by that at 16 min, suggesting the completion of the Wolff rearrangement. The concentration of the DNQMA−HEMA/DMF solution is 10 mg mL^{-1}.

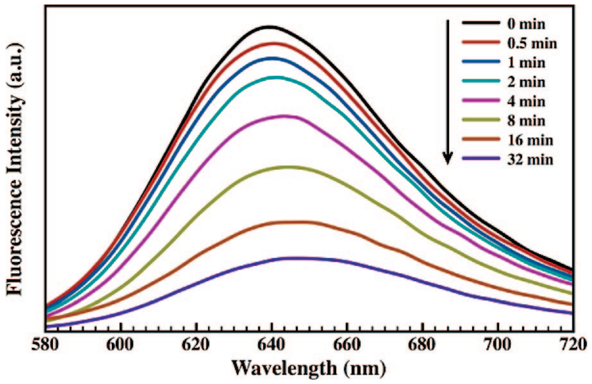


Figure 4. Time-dependent fluorescence emission spectra ($\lambda_{ex} = 550$ nm) of Nile red-loaded vesicles in the aqueous solution. The concentration of the DNQMA−HEMA/DMF solution and NR/DMF solution is 1 and 0.01 mg mL^{-1}, respectively.

we maintain that it is possible for random copolymer DNQMA−HEMA to evolve different morphologies of nanoassemblies. To our knowledge, this is the first demonstration of continuous morphological transitions of self-assemblies from random copolymer by simply changing the solvent quality. In our case, the nanoassemblies remained stable in dark for at least 2 months (Figure S7) and their size appeared quite uniform (Figure S8).

To determine whether the nanoassemblies could further evolve in morphology according to its intrinsic photosensitivity, which is attractive for controlled release, we irradiated the aqueous solution of large vesicles with laser light at 405 nm, at which DNQ molecules are expected to undergo the Wolff rearrangement, followed by TEM imaging at different time intervals. As shown in Figure 2b, the large vesicles gradually dissociated into globular hydrogel-like particles in water, which were structurally similar to the spherical micelles in Figure 2a, 20%. After UV exposure for 1 min, the vesicle periphery became loose and some fragments seemed to diffuse out. At 4 min, the vesicle became hollow while the fragments remained in center. At 16 min, the vesicle completely dissociated into separate uniform globular hydrogel-like particles. Upon irradiation, the substantial change in the hydrophilicity of DNQ moieties was associated with the chain rolling process in which the relatively weakly hydrophilic PHEMA backbone constituted the framework of hydrogel in its aqueous solution, while the more hydrophilic IC groups stabilize the particles. Further irradiation did not change the morphology of the globular particles substantially but drove the photoreaction to completion.

The light sensitivity of the random copolymers at 405 nm was confirmed by time-resolved UV−vis spectra of the brown DNQMA−HEMA/DMF solution (10 mg mL^{-1}) (Figure 3), which showed the decrease in intensity of the characteristic absorption peaks of DNQ/DMF solution at 310, 326, and 402 nm, accompanied by bubbling at the solution surface. After 8 min, the absorbance became saturated and the bubbling ceased, indicating the completion of the Wolff rearrangement of DNQ.

To demonstrate the potential application of the nanoassemblies in controlled release upon light irradiation, we prepared Nile red (NR)-loaded vesicles in the aqueous solution. Nile red, a fluorescent hydrophobic probe, which has been commonly used to stain phospholipids, has high fluorescence quantum yield in nonpolar and/or viscous solvents but very low quantum yield in water. As seen in Figure 4, the emission intensity of NR-loaded vesicle aqueous solution decreased dramatically with the increase of the irradiation time, and the maximum emission peak red-shifted from 639 to 646 nm. In a control experiment, the fluorescence intensity of the NR/DMF solution with the same concentration remained unchanged (Figure S9). Therefore, the decrease in emission in Figure 4 is attributed to the light-triggered release of NR molecules from vesicles into water.

In summary, we have synthesized photoresponsive random copolymers with amphiphilic nature. We demonstrate continuous morphological transitions of macromolecular nanoassemblies from spherical micelles through hollow tubes and wormlike rods to large vesicles simply by adding water. Upon UV irradiation, the vesicles were disintegrated into spherical particles, releasing the encapsulated fluorescent dye. We currently explore the possibility of reversing the sequence from vesicles through rods to micelles step-by-step in a mixed solvent under light. We believe that the study of self-assembly of amphiphilic random copolymers and their morphological transitions opens a completely new yet simple and robust route for construction of functional soft assemblies, which potentially could offer a broader range of morphologies and functions. Incorporation of light-responsive moieties in the assemblies will further provide useful means for site-specific release of dyes, drugs, and nutrients.

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Supporting Information Available: Experimental procedure; characterization of PHEMA, DNQMA−HEMA, and nanoaggregates. This material is available free of charge via the Internet at http://pubs.acs.org.

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