

A New Design for Light-Breakable Polymer Micelles

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Amphiphilic block copolymers in aqueous solution can self-assemble into a variety of micellar aggregates. Much current interest focuses on the exploitation of polymer micelles as nanocarriers of biologically active agents such as drugs.¹ In this regard, polymer micelles that are responsive to environmental changes, such as pH² and temperature,³ or can be disrupted by external stimuli⁴ are desirable. Most research efforts are being dedicated to pH-sensitive polymer micelles, exploring the fact that tumor tissues are slightly acidic (pH \approx 6.8) and the endosomal and lysosomal compartments of cells have even lower pH (pH \approx 5–6) with respect to the physiological pH, 7.4.^{2a} One demonstrated strategy is to incorporate acid-labile bonds in the hydrophobic block, whose breaking in acidic conditions increases the hydrophilicity of the block and thus disrupts the micelle.^{2a}

Polymer nanocarriers that can be disrupted by light are worth being explored. It is conceivable that if the release of encapsulated agents is triggered only by light, the time and the location of release are determined by when and where irradiation light is applied. To date, however, the use of light as an external stimulus to disrupt polymer micelles has been largely unexploited. Only recently, we have reported the synthesis of an amphiphilic diblock copolymer whose core-shell micelles and vesicles can be disrupted on irradiation by UV light and reformed by subsequent visible light exposure.⁵ The hydrophobic block of this system is a side-chain liquid crystalline polymethacrylate with azobenzene mesogens (PAzo), while the hydrophilic block is a random copolymer of poly(*tert*-butyl acrylate-*co*-acrylic acid) (*t*BA-AA). An optical plasticization of the compact micelle core and a change in polarity of the hydrophobic block, as a result of the *trans*-*cis* photoisomerization of azobenzene mesogens, were suggested to be at the origin of the observed photoresponse of polymer micelles.^{5,6} However, azobenzene polymer-based micelles cannot all be disrupted by light,⁷ since several structural parameters of the polymer, such as the block lengths and the functional groups on azobenzene moiety, can make the actual change in the hydrophilic/hydrophobic balance, under UV light exposure, insignificant and fail to result in micelle dissociation. It is therefore of interest to develop more general, effective, and robust approaches that allow polymer micelles to be disrupted by light. Herein, we report on such a new design strategy and demonstrate the straightforward light-induced breaking of polymer micelles.

Figure 1a schematically illustrates the strategy. The micelle core-forming hydrophobic block contains a photolabile chromophore as a pendant group; on UV light irradiation, chemical bond breaking detaches the chromophore from the polymer and transforms the hydrophobic block into a hydrophilic block, which leads to the dissociation of polymer micelles. To investigate the strategy, we have used atom transfer radical polymerization (ATRP) to prepare a novel amphiphilic diblock copolymer whose structure is shown in Figure 1b. The hydrophilic block is poly(ethylene oxide) (PEO), while the hydrophobic block is a polymethacrylate bearing pyrene moiety in the side group (PPy). In aqueous solution, the photo-

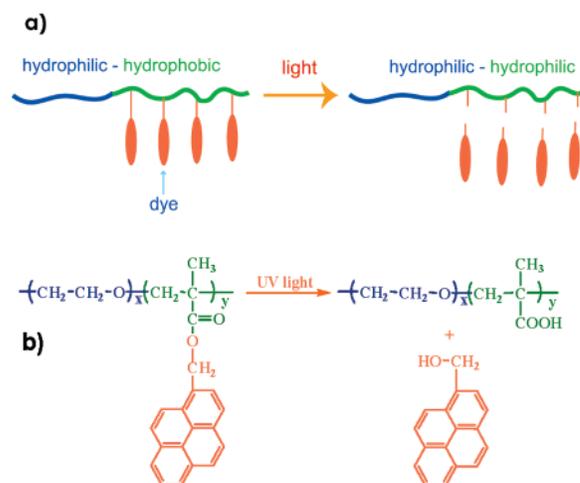


Figure 1. (a) Schematic illustration of light-induced detachment of dye pendant groups resulting in the hydrophobic-to-hydrophilic switch. (b) Chemical structure of the pyrene-containing amphiphilic diblock copolymer and its photosolvolysis under UV light irradiation.

solvolysis of pyrenylmethyl esters under UV light irradiation gives rise to the cleavage of 1-pyrenemethanol,⁸ which converts the ester groups to carboxylic acid groups and the hydrophobic PPy to hydrophilic poly(methacrylic acid) (PMA). Using the literature method,⁹ we prepared two PEO macroinitiators of molecular weights of 2000 and 5000 g mol⁻¹, corresponding to 45 and 112 EO units respectively, and used them to polymerize 1-pyrenemethyl methacrylate to grow the PPy block. Several PEO-*b*-PPy diblock copolymer samples were obtained with different compositions (determined from ¹H NMR) and relatively narrow polydispersity (<1.4, from GPC using polystyrene standards). For all samples, polymer micelles were observed under various preparation conditions, including slow addition of water in a THF solution of the polymer. The results shown in this communication were obtained with a sample of PEO-*b*-PPy composed of 45 EO and 72 Py units.

Scanning (SEM) and transmission electron microscope (TEM) observations confirmed the complete breaking or dissociation of polymer micelles in solution upon UV light irradiation. An example of SEM observation is shown in Figure 2a. In this experiment, PEO-*b*-PPy was dissolved in THF with an initial polymer concentration of 0.25 mg mL⁻¹; then 15 wt % of deionized water was added dropwise to the solution under stir to induce polymer micellization. After dilution with water, part of the micellar solution was cast on a silicon wafer and dried. Another part of the solution, \sim 3.5 mL placed in a quartz cuvette, was exposed to UV light for 15 min (UV light generated by a spot-curing system combined with a UV filter centered at 365 nm; total intensity \sim 2 W) before being cast and dried on silicon wafer for SEM observation. Figure 2a shows the SEM images obtained from the two solutions. Polymer core-shell micelles were formed in the solution without exposure to UV light, with an average diameter around 15 nm. By contrast,

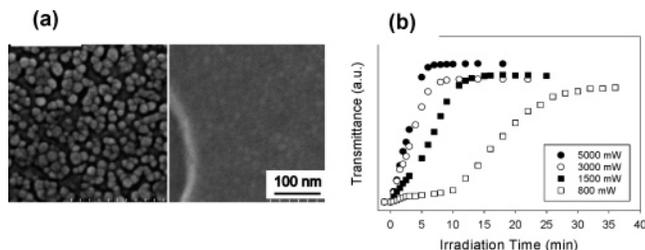


Figure 2. (a) SEM images showing micelles formed by PEO-*b*-PPy (left) and the dissociation of micelles after UV light irradiation of the micellar solution (right). (b) Optical transmittance vs time for the micellar solution under UV irradiation of various intensities.

no micelles remained in the solution subjected to UV light exposure. By recording the optical transmittance of a probe light (He–Ne laser, 633 nm, 2 mW) through the micellar solution under UV light irradiation, the process of light-induced breaking of micelles can be monitored in situ. Figure 2b shows the results obtained with a micellar solution exposed to different intensities of UV light. For this experiment, the micellar solution obtained by adding 15 wt % of water in the THF solution was not diluted using water to allow cleaved pyrene moieties to remain soluble in the solution. As micelles are dissociated, the turbidity of the solution decreases, and the transmittance increases. Figure 2b shows that the micelle-breaking process becomes faster as the intensity of UV light increases. At the highest intensity used, i.e., 5 W exposed to a solution of ~ 3 mL, it took about 5 min for micelles to be dissociated. ^1H NMR measurements showed that the degree of photosolvolysis increased with irradiation time. Fluorescence emission spectra of pyrene were also recorded. Before UV irradiation, as expected, the excimer emission peaked at about 478 nm, dominated with no observable monomer emission. After irradiation, the monomer emissions around 380–410 nm appeared, whose intensity increased with irradiation time, at the expense of excimer emission. These results clearly confirm that the detachment of pyrene moieties from the polymer, as a result of the photosolvolysis, was responsible for the disruption of micelles.

The encapsulation of a hydrophobic dye, Nile Red, by PEO-*b*-PPy micelles and the UV light-induced release was also investigated. In this experiment, Nile Red was first dissolved in a THF solution of PEO-*b*-PPy (polymer concentration, 0.06 mg mL^{-1} ; 6 wt % of Nile Red with respect to the amount of polymer); then water was added dropwise to induce the aggregation; afterward, about 4-fold volume of water was added to quench the micelles and THF was removed by evaporation (solution under stir warmed to 40°C). Figure 3a shows that the encapsulation, or solubilization, of Nile Red by micelles made the micellar solution appear pink. After UV light irradiation, the pink color disappeared; the turbidity of the solution also increased due to the released Nile Red and cleaved pyrene moieties that are both insoluble in water. Given in Figure 3b are fluorescence emission spectra of the micellar solution with encapsulated Nile Red before and after UV light exposure (excitation wavelength, 375 nm); for comparison, the emission spectrum of the micellar solution without Nile Red, prepared under the same conditions, is also shown. Without Nile Red added, there is only the excimer emission of pyrene at ~ 478 nm. While for the micellar solution containing Nile Red, the same excitation at 375 nm, where Nile Red has no absorption, results in the fluorescence emission of Nile Red centered at ~ 620 nm, with the excimer emission of pyrene reduced drastically. Considering the significant overlap of the emission spectrum of pyrene excimer and the absorption spectrum of Nile Red, Figure 3b suggests the occurrence

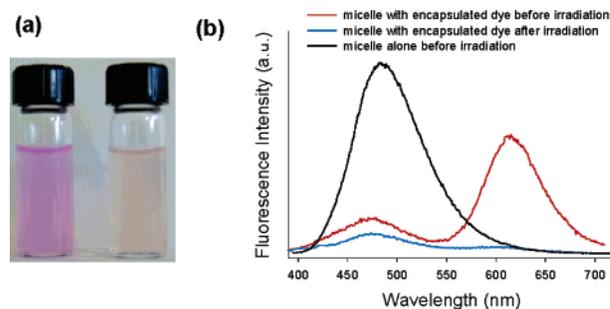


Figure 3. (a) Photos showing aqueous PEO-*b*-PPy micellar solution equilibrated with the hydrophobic dye of Nile Red before (left) and after (right) UV light exposure. (b) Their fluorescence emission spectra compared to that of the nonirradiated micellar solution containing no Nile Red.

of nonradiative energy transfer (NRET) between the two dyes, which indicates the close distance between them as a result of the encapsulation of Nile Red by the core of the hydrophobic PPy block. The release of Nile Red and the cleavage of 1-pyrenemethanol were revealed by drastic changes in their fluorescence emission after UV irradiation, both compounds being insoluble in water.

In conclusion, we present a novel and effective approach to designing amphiphilic block copolymers that can form light-breakable polymer micelles in solution. The design strategy, which is based on the photolysis of a photolabile chromophore on the hydrophobic block, is general and can readily be applied to many chromophores or dyes. We are currently investigating amphiphilic block copolymers bearing chromophores that can be photolyzed by near-infrared light (NIR) through two-photon absorption. Since IR light is less damaging to cells and tissues and has deeper penetration depth due to reduced absorption and scattering by biological substances and water, NIR light-dissociable polymer micelles are more suitable to biomedical applications.

Acknowledgment. Financial support from the Natural Sciences and Engineering Research Council of Canada and le Fonds québécois de la recherche sur la nature et les technologies of Québec is acknowledged. We also thank Prof. Pierre Harvey (Sherbrooke) for the use of the spectrofluorometer.

Supporting Information Available: Block copolymer synthesis, UV–vis, fluorescence, ^1H NMR, GPC, and TEM measurements. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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JA0521019