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Temperature-Driven Oxygenation Rate Control by Polymeric Photosensitizer

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The design and development of photoreaction systems capable of promoting organic transformations in an economically and environmentally friendly way is one of the biggest challenges in chemistry.[1] Such convenient systems must be able to control the photoreaction rate easily and reversibly. An easy way is to vary the light intensity absorbed by reactants (which involves turning up/down the intensity or varying the distance of reactant from light source). In contrast to these mechanical ways, the reaction rate can also be controlled by chemical ways: change solvent[2] and add a third component to the reaction mixture.[3] These principal ways, however, control the rate irreversibly. The development of systems enabling reversible photoreaction rate control by simple external stimuli without contaminating the reaction mixture is one of the most important issues to be addressed.

Our system presented here employs *temperature*, a basic and handy parameter, as the stimulus for reversible rate control. We use a polymeric photosensitizer, poly(NIPAM-*co*-BP), consisting of *N*-isopropylacrylamide (NIPAM)[4] and benzophenone (BP)[5] units as the thermosensitive and photosensitizing parts (Figure 1A). The photoexcited BP unit (^{3}BP*) produces singlet oxygen ($^1O_2$) via an energy transfer to O_2 (Figure 1B).[5] Here we report that this simple polymer acts as the first sensitizer, enabling *reversible photooxygenation rate control by temperature*. It is well-known that polyNIPAM in water shows a reversible *coil*-to-*globule* phase transition, associated with hydration/dehydration of the polymer chain by temperature.[4] This property has been applied to various materials: enzymatic reactor,[6a] drug delivery system,[6b] fluorescent device,[6c] catalyst,[6d] and adsorbent.[6e] Various polymers bearing a photosensitizing molecule had been proposed so far;[7] however, none of the systems had been utilized for thermal control of the photoreaction rate. We describe here that this unprecedented function is driven by a temperature-controlled self-assembly of the polymer, which cleverly controls the stability and diffusion of $^1O_2$ and the location of substrate.

Poly(NIPAM$_x$-*co*-BP$_y$) ($x/y = 0.94/0.06$) is easily prepared by a copolymerization of NIPAM and 4-allyloxyBP with AIBN.[8,9] Oxygenation activity was estimated with the transformation of phenol **1** to *p*-benzoquinone **2** (Figure 1B), a typical $^1O_2$ oxygenation reaction.[5,7e] The reaction was carried out by photoirradiation ($\lambda > 320$ nm) to an O_2-saturated aqueous solution (pH 10) containing **1** (10 μmol) and poly(NIPAM-*co*-BP) (0.2 mg containing 0.1 μmol BP and 1.6 μmol NIPAM units).[8]

Photoirradiation of **1** with poly(NIPAM-*co*-BP) affords **2** as a sole product at all tested temperatures, as does 4-hydroxyBP (HBP; 0.1 μmol),[9] a reference water-soluble sensitizer. Figure 2 summarizes changes in the yields of **2** with temperature. With HBP (white), the yield increases slightly as the temperature rises, as is usually observed for $^1O_2$ oxygenation.[5a] This is because a rise in temperature accelerates the diffusion of HBP, O_2, and **1**, resulting in an enhancement of $^1O_2$ formation and oxygenation of **1**.[10] In contrast, poly(NIPAM-*co*-BP) (black) shows a drastic increase in the yield of **2** with a rise in temperature up to 17 °C, while showing a decrease at >22 °C. To the best of our knowledge, this is the first photoreaction system showing a temperature-dependent off−on−off-type activity profile.

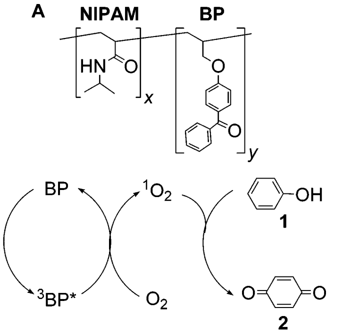

Figure 1. (A) Structure of poly(NIPAM-*co*-BP), where each unit is randomly arranged along the chain. (B) Sensitized $^1O_2$ oxygenation.

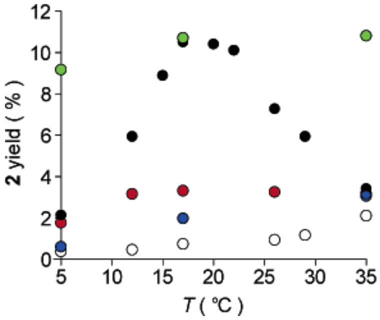

Figure 2. Temperature-dependent change in **2** yield (3 h) in O_2-saturated aqueous solution (pH 10). The systems are: (white) 0.1 μmol HBP, (red) 0.1 μmol HBP with 0.2 mg polyNIPAM, (blue) 0.1 μmol HBP with 1.6 μmol NMA, (green) 0.1 μmol HBP with 8 μmol NMA, and (black) 0.2 mg poly(NIPAM-*co*-BP).

As shown in Figure 2 (blue), HBP with a monomer amide (*N*-methylacetoamide: NMA; 1.6 μmol) shows higher **2** yield than does HBP alone (white). This is because basic amide promotes deprotonation of **1** (formation of a phenoxide anion) and, hence, accelerates the electrophilic addition of $^1O_2$.[11] The **2** yield is, however, much lower than that obtained with poly(NIPAM-*co*-BP) (black). HBP with 5-fold molar excess NMA (8 μmol; green) shows the same high **2** yield as does the polymer at 17 °C; but, the yields at 5 and 35 °C are also high, giving a flat profile. HBP with BP-free polyNIPAM[8] (0.2 mg; red) shows higher **2** yield than does HBP alone, but still gives a flat profile.

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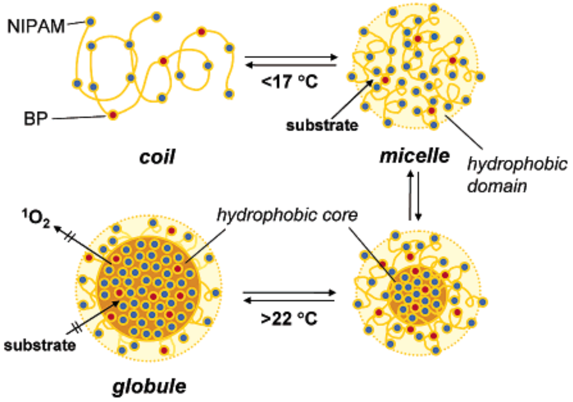

Figure 3. Change in structure of poly(NIPAM-*co*-BP) in water.

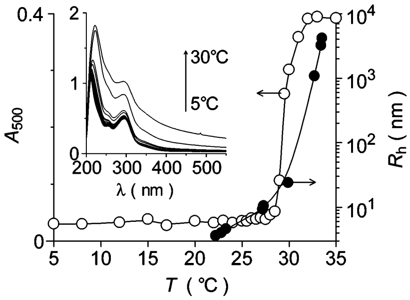

Figure 4. Temperature-dependent change in turbidity (A_{500}) and hydrodynamic radius (R_h) of poly(NIPAM-*co*-BP) in aqueous solution (pH 10). (Inset) Change in absorption spectra of the solution.

The off−on−off activity of poly(NIPAM-*co*-BP) is driven by a heat-induced phase transition of the polymer from *coil* to *micelle*, and then to *globule* state (Figure 3). The micelle contains a *hydrophobic domain* capable of lengthening $^1O_2$ lifetime, leading to oxygenation enhancement, while the globule contains a *hydrophobic core* capable of eliminating **1** and suppressing $^1O_2$ diffusion to bulk water, leading to oxygenation suppression. Figure 4 (white) shows temperature-dependent change in turbidity of water containing poly(NIPAM-*co*-BP); an obvious increase at >29 °C implies that almost all of the polymer aggregates strongly at >29 °C (globule state).[4] ^{1}H NMR analysis of the polymer in D_2O shows a lower-field resonance shift of C*H* adjacent to NH group as the temperature rises from 5 to 17 °C (Figure S1[8]),[12] indicating that *loose* aggregation occurs at 5−17 °C (micelle state; Figure 3), and the hydrophobic domain becomes more hydrophobic as the temperature rises. At >17 °C, the C*H* resonance shifts further, along with the intensity decrease (Figure S1[8]); this is due to the removal of D_2O associated with the strong polymer aggregation.[12a] Dynamic light scattering (DLS) analysis (Figure 4 and S2[8]) of the polymer solution detects a formation of the hydrophobic core at >22 °C (det. limit, 3 nm),[12] implying that strong aggregation occurs partially at about >22 °C (Figure 3).

The **2** yield increase at 5−17 °C (Figure 2) is triggered by the heat-induced growth of the hydrophobic domain, lengthening the $^1O_2$ lifetime.[5,13] This is confirmed by a $^1O_2$-trapping ESR analysis with 2,2,6,6-tetramethylpiperidine (TEMP). As shown in Figure 5A, photoirradiation of the polymer in an aerated solution with TEMP[8] gives TEMP−$^1O_2$ spin adduct signals ($a^N = 17.3$ G, $g = 2.0053$),[14] as is also the case for HBP. Figure 5B shows $^1O_2$ quantum yield (Φ_{1O2}), determined by double integration of the adduct signal.[14b] The Φ_{1O2} obtained with the polymer (black) actually increases as the temperature rises from 5 to 17 °C; this agrees well with the **2** yield profile (Figure 2). In contrast, the Φ_{1O2} for HBP−NMA (blue) and HBP−polyNIPAM (red) systems scarcely change at this temperature range; these also agree with the yield profile. These indicate that, from 5 to 17 °C, the growth of the hydrophobic domain within poly(NIPAM-*co*-BP) lengthens the $^1O_2$ lifetime more, resulting in oxygenation enhancement.

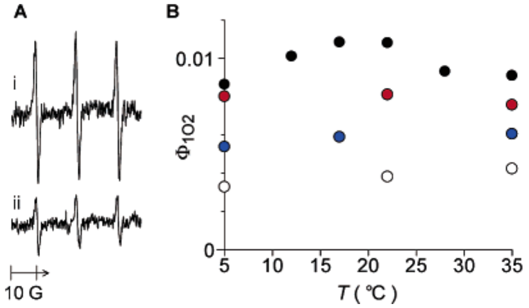

Figure 5. (A) ESR spectra of TEMP−$^1O_2$ spin adduct obtained by photoirradiation (at 17 °C) to an aerated solution (pH 10) containing TEMP with (i) poly(NIPAM-*co*-BP) and (ii) HBP. (B) $^1O_2$ quantum yield (Φ_{1O2}) obtained by double integration of the lowest magnetic field signal of the adduct, where Rose Bengal was used as reference ($\Phi_{1O2} = 0.75$ (at 25 °C); ref 14b). The systems used are identical to those in Figure 2.

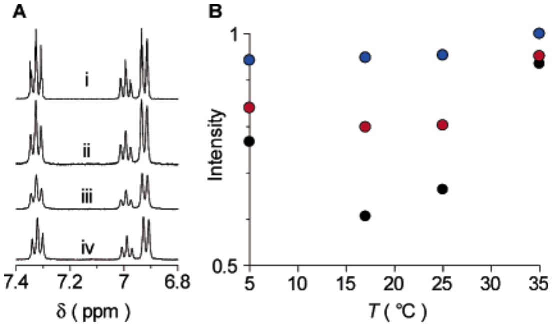

Figure 6. (A) ^{1}H NMR spectra of **1** in D_2O at (i) 35 °C and at (ii) 35, (iii) 17, and (iv) 5 °C with poly(NIPAM-*co*-BP). (B) Signal intensity of ^{1}H NMR spectra of (black) **1** measured with poly(NIPAM-*co*-BP), (red) TEMP measured with poly(NIPAM-*co*-BP), and (blue) HBP measured with polyNIPAM. The intensity was determined by integration of all of the C*H* resonances of **1**, TEMP, and HBP, where the intensities of **1**, TEMP, and HBP measured at 35 °C without polymers were set as 1.

Further confirmation of the mechanism was made by ^{1}H NMR analysis of **1** with poly(NIPAM-*co*-BP). Figure 6A shows a change in the C*H* resonance of **1** with temperature. The signal measured at 17 °C is obviously weaker than that at 5 and 35 °C; this clearly indicates that **1** exists within the hydrophobic domain of the polymer at 17 °C. Figure 6B (black) shows change in the signal intensity of **1**, determined by integration of the signal. The intensity decreases as the temperature rises from 5 to 17 °C, meaning that **1** exists within the domain at 5−17 °C, and the domain becomes more hydrophobic as the temperature rises. This suggests that the heat-induced growth of the hydrophobic domain lengthens the lifetime of $^1O_2$, which oxidizes **1** within the domain effectively, resulting in the oxygenation enhancement at 5−17 °C. However, the Φ_{1O2} increase at 5−17 °C obtained with the polymer (Figure 5B, black) is lower than that expected from the **2** yield increase (Figure 2). As shown in Figure 6B (red), signal intensity of TEMP when measured with the polymer indicates that hydrophobicity around TEMP is much lower than that around **1**. This suggests that TEMP does not exist sufficiently within the domain,[15] leading to insufficient reaction with $^1O_2$ formed within the domain. Signal intensity of HBP measured with polyNIPAM[16] (Figure 6B, blue) does not decrease, meaning that HBP exists mainly in bulk water.[15] Almost no enhancement of the **2** yield in HBP−polyNIPAM system (Figure 2) is, therefore, due to no lifetime enhancement of $^1O_2$ formed in bulk water.

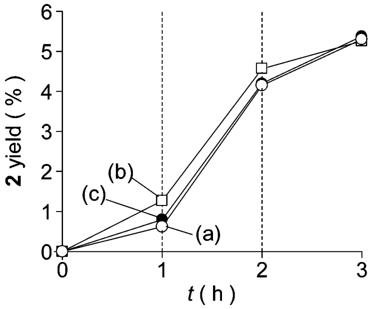

Figure 7. Change in **2** yield with time in poly(NIPAM-*co*-BP) system, where the reaction temperature is changed after each hour: (a) 5 → 17 → 35 °C, (b) 35 → 17 → 5 °C, and (c) 5 → 17 → 35 °C. Run (c) is carried out with the polymer recovered after run (a). The recovery process is heating the sample to 40 °C, followed by centrifugation (5 min, 2×10^4 rpm).

At >22 °C (Figure 2), the **2** yield obtained with poly(NIPAM-*co*-BP) decreases as the temperature rises. This is explained by the heat-induced phase transition of the polymer from *micelle* to *globule* containing a hydrophobic core, which leads to elimination of **1** and suppression of ${}^1O_2$ diffusion to bulk water. At >22 °C, the polymer aggregates strongly, and the size of the hydrophobic core increases exponentially as the temperature rises (Figure 4, black). As shown in Figure 6B, signal intensity of **1** measured with the polymer increases at >22 °C, which is consistent with the growth of the hydrophobic core. This indicates that **1** does not exist within the core. In contrast, O_2 can diffuse within the core and form ${}^1O_2$.[17] The lifetime of ${}^1O_2$ (τ_{1O2}) formed within the hydrophobic core must be longer than in bulk water (τ_{1O2} in water is $< 5\ \mu$s).[13,17] However, ${}^1O_2$ diffusion within the core is restricted more[17] (diffusion coefficient, D_{1O2}, $<5 \times 10^{-7}$ cm^2 s^{-1}; Table S2[8]) than in bulk water ($>1 \times 10^{-5}$). The limited diffusion of ${}^1O_2$ to bulk water by the rigid core may, therefore, lead to the **2** yield decrease at >22 °C. Rough calculation of the diffusion distance of ${}^1O_2$ [$(D_{1O2}\tau_{1O2})^{1/2}$] formed within the core within its lifetime, when using the values of $D_{1O2} = 5 \times 10^{-7}$ cm^2 s^{-1} and $\tau_{1O2} = 31\ \mu$s (value in *n*-hexane; Table S1[8]), gives only 39 nm. As shown in Figure 4, the core diameter at 22 °C is only 3.5 nm but reaches 1 μm at 32 °C. The core size increase agrees with the **2** yield decrease (Figure 2). ESR analysis (Figure 5B, black) confirms the decrease in Φ_{1O2} at >22 °C. These findings clearly suggest that the heat-induced strong aggregation of the polymer (formation and expansion of the hydrophobic core) suppresses the ${}^1O_2$ diffusion to bulk water, leading to **2** yield decrease at >22 °C (Figure 3),[18] where only ${}^1O_2$ formed near the outer surface of the globule state polymer can react with **1**.

Figure 7 shows change in the **2** yield with time, obtained with poly(NIPAM-*co*-BP), where the reaction temperature is changed after each hour. The data clearly show that (i) the oxygenation rate is changeable by temperature and (ii) the rate obtained at the same temperature is identical regardless of the temperature sequence (5 → 17 → 35; 35 → 17 → 5 °C). These results indicate that the polymer can control the oxygenation rate *reversibly*. Another notable feature of the polymer is the high reusability with a simple recovery process: heating the reaction mixture to 40 °C followed by centrifugation (5 min, 2×10^4 rpm) affords >98% polymer recovery, and the recovered polymer shows the same activity as does the virgin polymer (run c).

In summary, we have found that a polymeric photosensitizer, poly(NIPAM-*co*-BP), reversibly controls the ${}^1O_2$ oxygenation rate by temperature, which is driven by a temperature-controlled self-assembly of the polymer. The simple photoreaction system proposed here exhibits significant advantages: (i) additive-free, (ii) high reusability, and (iii) high operability (reaction is operated at around room temperature). This basic concept for polymer design may contribute to the development of economically and environmentally friendly phototransformation processes and to the design of more efficient photosensitizing materials.

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Supporting Information Available: Materials, methods, Tables S1 and S2, and Figures S1−S8. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) The log *P* values for **1**, TEMP, and HBP are 1.64, 1.67, and 2.85, respectively. The lower uptake of TEMP and HBP into the hydrophobic domain of poly(NIPAM-*co*-BP) or polyNIPAM than that of **1** may be attributable to the bulky structure of TEMP and HBP (Figure S3).
(16) BP-free polyNIPAM shows obvious turbidity increase at 32 °C and hydrophobic core formation at >24 °C (Figures S5 and S6).
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(18) As shown in Figure 4 (inset), BP unit still absorbs light (at around 300 nm) at >22 °C, where transmittance of the solution scarcely decreases (85% at 5 °C and 82% at 35 °C; Figure S4). These facts rule out the decrease in the incident light absorption of the BP unit, associated with the polymer aggregation, as the major factor for **2** yield decrease.

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