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Oxidation-Accelerated Hydrolysis of the Ortho Ester-Containing Acid-Labile Polymers

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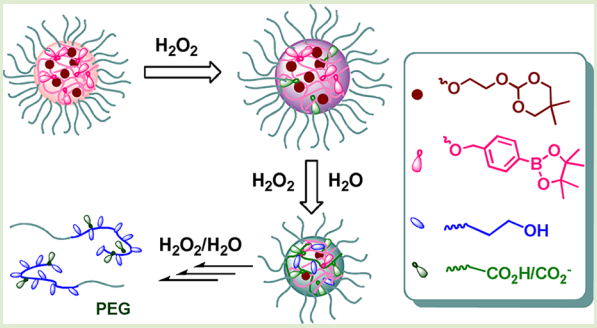
Supporting Information

ABSTRACT: We report a versatile method to tune the hydrolysis of the ortho ester-containing block copolymers by covalently incorporating oxidation-sensitive phenylboronic ester units. A series of block copolymers which contain a polyethylene glycol (PEG) block and a hydrophobic segment composed of different amounts of pendent ortho ester and phenylboronic ester groups were synthesized. These copolymers can self-assemble into narrowly dispersed micelle-like nanoparticles in phosphate buffer. The kinetics of phenylboronic ester oxidation and ortho ester hydrolysis in the nanoparticles were studied at different pH and H_2O_2 concentration. The results indicated that the phenylboronic ester oxidation rate was faster than the ortho ester hydrolysis rate at neutral pH, and both processes were accelerated with increasing H_2O_2 concentration. Nanoparticles which are extremely sensitive to the biorelevant concentration of H_2O_2 (50 μM) at pH 7.4 were obtained, suggesting great promise for inflammation-specific drug delivery.



Poly(ortho ester)s (POEs) represent an important family of pH-sensitive polymers. The backbone-degradable POEs have been developed and studied systematically in the past four decades because of their promising performance such as tunable degradation kinetics, ease of manufacture, good biocompatibility, and so forth.[1] Cationic polymers containing ortho ester units in the backbone were also reported for nonviral gene delivery.[2] Besides, in recent years, acid-labile polymers with pendent cyclic ortho ester groups have been synthesized and investigated on their potential applications as intelligent vehicles for anticancer drug delivery.[3] In general, the pH-dependent hydrolysis rates of ortho esters depend mainly on their chemical structures;[4] however, the degradation behavior or hydrolysis kinetics of the ortho ester-based acid-labile polymers are also influenced by additional factors including hydrophilic/hydrophobic balance,[4c,5] constitutional and stereostructure,[6] physical addition of acidic or basic excipients,[7] and covalently incorporating latent acidic components.[8]

Reactive oxygen species (ROS), at the appropriate concentrations, play important roles in a wide range of physiological processes such as oxidative signaling and fighting against infectious agents. However, overproduction of ROS is also associated with many diseases including inflammatory pathologies, tumors, and cardiovascular and degenerative diseases.[9] In recent years, various oxidation-responsive polymers and the relevant nanoparticles including poly(propylene sulfide)s, poly(dithioacetals), arylboronic ester- or selenium-containing polymers, polyoxalate nanoparticles, oligo(proline)-cross-linked scaffolds, and ferrocene-based polymers have been prepared and studied on their versatile properties.[9c,f,10] These polymers show great potential for ROS detection, inflammation-specific drug delivery, polymeric vaccines, and polymer-based antioxidants.[10b,e,11] Besides ROS overproduction at some inflammation sites and in the phagosomes, lower pH is another biological feature of most endosomes or phagosomes.[12] Therefore, it is interesting to develop dual-responsive polymers that respond to both pH and ROS, especially systems that work synergistically. Recently, Almutairi and co-workers reported a type of logic gate nanoparticle based on polythioether ketal polymers, the degradation kinetics of which was notably accelerated with combined oxidative condition and acidity.[13] However, a relatively high concentration of H_2O_2 (100 mM) was necessary to acquire an effective responsiveness. In this work, we report a new type of pH/oxidation dual-responsive amphiphilic block copolymer composed of ortho ester and phenylboronic ester motifs. In the copolymer nanoparticles, pH-dependent hydrolysis of the ortho ester can be accelerated by H_2O_2 which oxidizes the phenylboronic ester to the catalytic carboxylic acid (Scheme 1).

Since the ortho ester and the phenylboronic ester are extremely sensitive to mild acid and low concentration of H_2O_2,[10b,c,14] respectively, the degradation rates of the dual-responsive nanoparticles can be easily tuned by changing the

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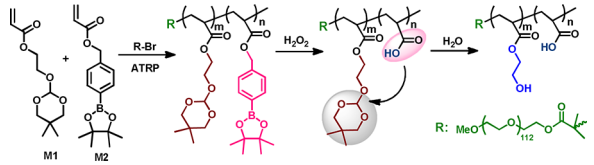
Scheme 1. Preparation of the Block Copolymers, Their Oxidation, and Hydrolysis Reactions



copolymer compositions, making the nanoparticles versatile as carriers for imaging of or drug delivery to the inflammation sites as well as for a nanoparticulate-based vaccine. Furthermore, this work provides an additional approach to modulate degradation or hydrolysis kinetics of the ortho ester-based polymers.

Ortho ester-containing acid-labile acrylic monomer (**M1**) was prepared following a published procedure.[14] Oxidation-sensitive acrylic monomer (**M2**) was synthesized by the reaction of acryloyl chloride and 4-(hydroxymethyl)-phenylboronic acid pinacol ester, and the structure was confirmed by NMR and FT-IR measurements (Figure S1, Supporting Information). Monomer **M2** can be rapidly oxidized by H_2O_2, generating boronic acid, pinacol, acrylic acid, and 4-(hydroxymethyl)phenol through several sequential steps (Figure S2, Supporting Information). When **M2** was oxidized by H_2O_2 in phosphate buffer (PB), the in situ formed *p*-quinone methide first reacted with HPO_4^{2-} (or $H_2PO_4^-$) to form the intermediate 4-hydroxybenzyl phosphate, which gradually hydrolyzed into 4-(hydroxymethyl)phenol. In pure D_2O without PB, by contrast, *p*-quinone methide reacted directly with water to form 4-(hydroxymethyl)phenol (Figure S3, Supporting Information). In the absence of H_2O_2, monomer **M2** only gradually decomposed into 4-(acryloxymethyl)phenylboronic acid in PB, releasing pinacol, and no oxidation products such as acrylic acid and 4-(hydroxymethyl) phenol were formed (Figure S4, Supporting Information).[15]

Atom transfer radical copolymerization (ATRP) of monomers **M1** and **M2** was carried out by using $mPEG_{113}$−Br as a macroinitiator. By changing the feed ratio of the two monomers, a family of block copolymers (**P1**−**P6**) was synthesized. They had comparable molecular weights but with different compositions of ortho ester and phenylboronic ester (Table 1 and Figures S5 and S6, Supporting Information). These amphiphilic block copolymers self-assembled into narrowly dispersed micelle-like nanoparticles in PB by the solvent-displacement method (see the Supporting Information), except **P1** which formed aggregates with a bimodal size distribution (Table 1 and Figures S7 and S8, Supporting Information).

Table 1. Characterization and Properties of the Block Copolymers

	F1/F2[a]	Mn[a]	Mn[b]	PDI[b]	R_h (nm)[c]	R_g/R_h[c]
P1	100/0	18800	19200	1.19	33,136[d]	---
P2	96/4	14500	16500	1.24	27	0.78
P3	90/10	17300	19700	1.18	35	0.85
P4	80/20	17100	19500	1.21	26	0.86
P5	52/48	20700	21000	1.20	28	0.78
P6	0/100	18300	18100	1.20	33	0.79

[a]Molar ratio of **M1** to **M2** in copolymer and number-averaged molecular weight determined by ^{1}H NMR spectroscopy (Figure S6, Supporting Information). [b]Measured by GPC using polystyrene standards in THF. [c]Measured in PB (pH 7.6, 10 mM) with a polymer concentration of 0.1 mg/mL, 37 °C. [d]Bimodal distribution.

Oxidation kinetics of the phenylboronic ester and the oxidation-promoted ortho ester hydrolysis behaviors of the copolymer nanoparticles were first studied by ^{1}H NMR spectroscopy at pH 7.4 (300 mM deuterated PB). Representative time-dependent ^{1}H NMR spectra of the **P5** nanoparticle with 6-fold excess of H_2O_2 are shown in Figure 1. At 0 time

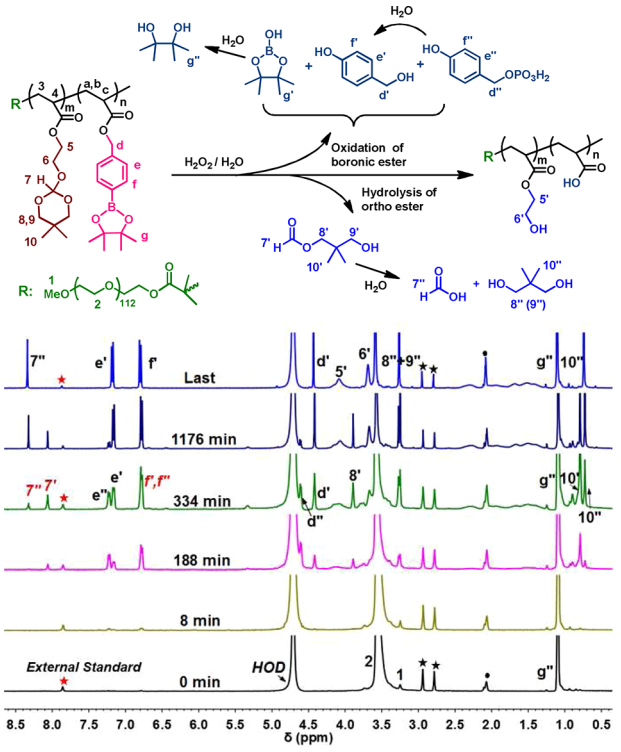


Figure 1. Time-dependent ^{1}H NMR spectra of copolymer **P5** (8 mg/mL) in deuterated phosphate buffer (pH 7.4, 300 mM) with 6-fold excess of H_2O_2 (molar ratio to **M2** unit in the copolymer, 64 mM) at 37 °C. The symbols of star and dot denote proton signals of DMF in the external standard capillary and the residual deuterated acetone, respectively.

point (no H_2O_2), the proton signals of the PEG block were clearly observed, whereas the signals of the hydrophobic segments were invisible, further supporting that polymer **P5** self-assembled into the micelle-like nanoparticles. It is noticed that the proton signal (g″ at ∼1.2 ppm) assigned to free pinacol was detected in the absence of H_2O_2, which is attributed to the unmasking of the phenylboronic ester into phenylboronic acid during the preparation process of the nanoparticles.[15] By strictly controlling the preparation conditions, the copolymer nanoparticles with comparable unmasking degrees of the phenylboronic ester, being 46% (**P2**), 40% (**P3**), 37% (**P4**), and 36% (**P5**), were prepared. Upon adding H_2O_2 to the nanoparticle dispersion, phenylboronic ester or its acid was quickly oxidized as indicated by the appearance of peaks at ∼6.8 ppm (f′ + f″) within 8 min, which was followed by the ortho ester hydrolysis to release 2,2-dimethyl-1,3-propanediol monoformate and its hydrolyzed product, formic acid (Figure 1). Finally, all proton signals of the oxidation and hydrolysis products were clearly observed. For the other copolymer nanoparticles, similar ^{1}H NMR spectra were obtained (Figure

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S9, Supporting Information). From these spectra, kinetic curves of the phenylboronic ester/acid oxidation and the ortho ester hydrolysis can be calculated.

Figure 2 shows the kinetics of **P2**−**P5** nanoparticles with 6-fold excess of H_2O_2. Both phenylboronic ester/acid oxidation

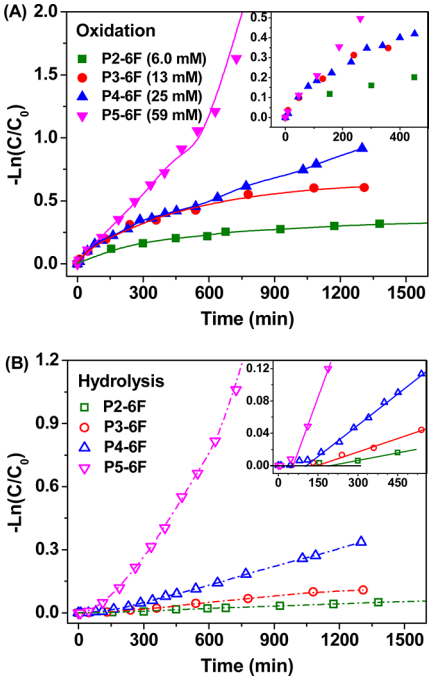

Figure 2. Kinetics of phenylboronic ester/acid oxidation by H_2O_2 (A) and ortho ester hydrolysis (B) of **P2**−**P5** nanoparticles at pH 7.4, 37 °C. "xF" in legend means the molar ratio of H_2O_2 to the **M2** unit in the copolymer nanoparticle. C_0 and C denote the initial and subsequent concentration of phenylboronic ester/acid or ortho ester, respectively.

and ortho ester hydrolysis follow the general order of **P5** > **P4** > **P3** > **P2**. For the same copolymer nanoparticle, the hydrolysis started later than the oxidation with a clear lag time being in the order of **P2** > **P3** > **P4** > **P5**, and in the following time, the oxidation was faster than the hydrolysis. However, in the absence of H_2O_2, no oxidation products were detected, and little ortho ester hydrolysis was observed in 24 h (Figure S10, Supporting Information). For copolymer **P1**, H_2O_2 did not influence the ortho ester hydrolysis, with no hydrolyzed products detected at pH 7.4 after incubation at 37 °C for 24 h (Figure S11, Supporting Information). These results can be rationally explained by the extreme oxidation sensitivity of phenylboronic ester/acid to H_2O_2 and the significant effect of hydrophilic/hydrophobic balance on the hydrolysis of the ortho ester.[4c,10b,c,16] As aforementioned, rapid oxidation of phenylboronic ester/acid and the subsequent self-immolative elimination result in carboxylic groups, which can increase the polarity of the microenvironment in the nanoparticles and facilitate the influx of water molecules, both accelerating the ortho ester hydrolysis.

The effect of H_2O_2 concentration on the kinetics of phenylboronic ester/acid oxidation and ortho ester hydrolysis of **P2** and **P5** nanoparticles was further studied. In each case, the oxidation or hydrolysis rate constants increased with the increasing H_2O_2 concentration, but not following a linear relationship (Figure 3). At the initial stage, the estimated rate

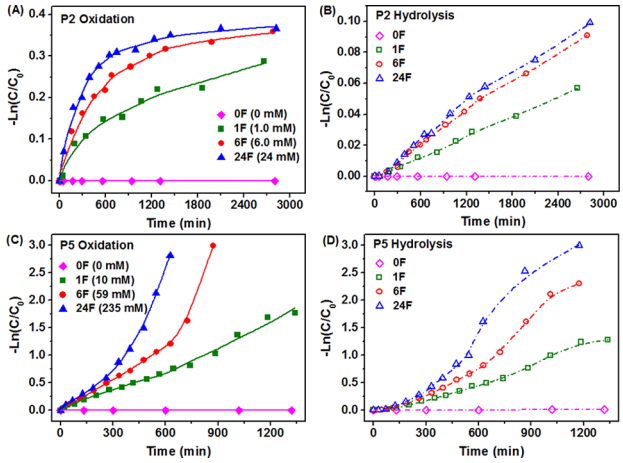

Figure 3. Effect of H_2O_2 concentration on kinetics of phenylboronic ester/acid oxidation (A, C) and ortho ester hydrolysis (B, D) of **P2** and **P5** nanoparticles at pH 7.4, 37 °C. "xF" in legend means the molar ratio of H_2O_2 to the **M2** unit in the copolymer nanoparticles.

constants increased less than 2.5 times as the concentration of H_2O_2 was raised by a factor of 24 (Figure S12, Supporting Information). Since the oxidation of phenylboronic acid follows a first-order kinetics to H_2O_2 in a homogeneous aqueous buffer,[17] and the subsequent self-immolative elimination proceeds very fast at pH 7.4 (Figure S2, Supporting Information), we speculate that the oxidation kinetics is mainly controlled by the diffusion process of H_2O_2 and H_2O into the copolymer nanoparticles.

When revisiting Figure 3A and 3C, we found that the oxidation of both **P2** and **P5** nanoparticles did not follow a first-order kinetics in the whole process. The oxidation rate constants of **P2** nanoparticles gradually decreased with time, and the oxidation almost ceased after 24 h (~30% conversion) at the highest H_2O_2 concentration used (Figure S13C, Supporting Information). In contrast, the kinetic curves of **P5** showed an upward deviation from first order and changed to approximately zero order as the concentration of H_2O_2 increased to 24-fold excess (Figure S13E, Supporting Information). These results are rationally attributed to the dramatic difference in composition of the two copolymers. In the case of **P5** having an approximately 1:1 molar ratio of phenylboronic ester/acid to ortho ester, the rapid oxidation of phenylboronic ester/acid can easily create interconnected hydrophilic channels which are essential for the nanoparticles to uptake water and H_2O_2 molecules. The subsequent hydrolysis of the ortho ester exerts a synergistic effect on both oxidation and hydrolysis processes by generating more hydrophilic channels in the nanoparticles. Copolymer **P2** contains only 4% of the phenylboronic ester units, most of which are likely isolated by the hydrophobic ortho ester units in the core of the nanoparticle. The unmasked phenylboronic acid units formed during the fabrication process are preferably enriched in a shell layer between the hydrophobic core and the PEG corona and easily oxidized (Figure S14, Supporting Information). The phenylboronic ester/acid units located deeper inside are difficult to contact with H_2O_2 and water due to the hydrophobic nature of the ortho ester units, showing a slowing oxidation rate.

Nile red (NR) is a hydrophobic, solvatochromic dye whose fluorescence quantum yield decreases with the increase in polarity of its microenvironment.[18] NR is often used as a

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fluorescent probe to monitor the degradation of nanoparticles.[3a,19] In this work, the degradation profiles of **P1**, **P4**, and **P5** nanoparticles were studied by monitoring the fluorescence intensity change (at the maximum wavelength) of NR at 37 °C (Figures S15 and S16, Supporting Information). For **P1** nanoparticles, little degradation was observed regardless of H_2O_2 presence or not. In contrast, H_2O_2 greatly enhanced the degradation of nanoparticles **P4** and **P5**. More boronic ester or higher H_2O_2 concentration can accelerate the degradation of the nanoparticles, being consistent with the ^{1}H NMR results. Particularly, **P5** nanoparticles were extremely sensitive to H_2O_2 with a significant release of NR even at the biorelevant concentration of H_2O_2 (50 μM), implying a great promise of the nanoparticles as oxidation-sensitive vehicles.[10c]

Since both the overproduction of ROS and the lower pH may coexist at some inflammation sites and in the phagosomes, it is essential to investigate the effect of pH on the degradation of the copolymers. Figure 4 shows the kinetic curves of

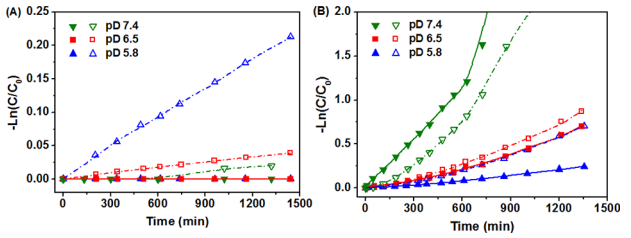

Figure 4. Kinetics of phenylboronic ester/acid oxidation (solid symbols) and ortho ester hydrolysis (empty symbols) in **P5** nanoparticles at different pHs at 37 °C, concentrations of H_2O_2: (A) 0 mM and (B) 59 mM (6-fold excess to the phenylboronic ester).

phenylboronic ester/acid oxidation and ortho ester hydrolysis of **P5** nanoparticles at different pHs with or without H_2O_2, as monitored by ^{1}H NMR spectroscopy. As expected, the hydrolysis of the ortho ester groups is faster at lower pH, and no oxidation product was formed in the absence of H_2O_2. Upon exposure to H_2O_2, however, **P5** nanoparticles showed the fastest kinetics of the ortho ester hydrolysis at pH 7.4, while the oxidation of phenylboronic ester/acid slowed down with the pH decrease (Figure S17, Supporting Information). These results indicate that the oxidation-promoting effect on the ortho ester hydrolysis is drastically pH-dependent. Although a lower pH is helpful for the hydrolysis of ortho ester, it is unfavorable to the self-immolative elimination which is a key step of the oxidation process.[20] We rationally speculate that the nanoparticle degradation, which is affected by both hydrolysis of the ortho ester and oxidation of the phenylboronic ester/acid, can be finely modulated by tuning the copolymer composition as well as by changing the concentration of H_2O_2 and/or pH of the buffer used.

In summary, we have developed a new type of pH/oxidation dual-responsive amphiphilic block copolymer composed of ortho ester and phenylboronic ester components. These copolymers could form micelle-like nanoparticles. Degradation of the nanoparticles can be finely modulated by tuning the copolymer composition, the external H_2O_2 concentration, and the pH of the buffer used. At neutral pH, hydrolysis of the ortho ester can be accelerated by H_2O_2 which oxidizes the phenylboronic ester to the catalytic carboxylic acid. This type of pH/oxidation dual-responsive nanoparticle may find application in the field of smart drug delivery after the toxicity of the degradation byproducts are fully evaluated.

■ ASSOCIATED CONTENT

Supporting Information

Experimental part, NMR and FT-IR spectra of M2, GPC curves of the copolymers, more ^{1}H NMR spectra, TEM results, NR emission spectra, and more kinetic curves. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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