UV-Responsive Degradable Polymers Derived from 1-(4-Aminophenyl)ethane-1,2-diol

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ABSTRACT: A UV-responsive polymer was prepared via condensation polymerization of 2-nitrobenzyl(4-(1,2-dihydroxyethyl)phenyl)carbamate and azalaic acid dichloride. When the polymer was irradiated with UV light, the nitrobenzyl urethane protecting group was removed and the deprotected aniline underwent spontaneous 1,6-elimination reactions, resulting in degradation of the polymer. Nanoparticles with encapsulated Nile Red were formulated with the degradable polymer and triggered burst release of Nile Red was observed when the nanoparticles were irradiated by UV light. © 2015 Wiley Periodicals, Inc. J. Polym. Sci., Part A: Polym. Chem. 2015, 53, 1161–1168

KEYWORDS: degradable materials; depolymerization; nanoparticles; photochemistry; polyester; self immolative; stimuli-sensitive polymer; triggered release

INTRODUCTION Polymers that can be degraded in response to external triggers have been used in many applications, such as controlled release, self-healing, tissue engineering, sensors, and smart surface coatings.1–15 Substantial effort has been devoted to developing degradable polymers with stimuli-responsive groups incorporated into the polymer backbones to control their degradation. Recently, there is growing interest in designing polymers whose degradation is controlled by the terminal or side-chain trigger-responsive groups.16–24 Representative examples include the self-immolative polymers developed by Shabat and coworkers that can be degraded through removal of the terminal trigger-responsive protecting group25,26 and the polymers developed by the Almutairi24,27–30 and Gillies groups17,31,32 with trigger-responsive domains placed on the side groups which control the polymer degradation. Inspired by these works, we recently designed 2,6-bis(hydroxymethyl)aniline (BHA), an analog of the key block of the self-immolative polymers ((4-aminophenyl)methanol), and used it to develop chain-shattering-polymers (CSPs)33 and chain-shattering polymeric therapeutics.34 By removing the pendant urethane protecting groups, CSPs undergo a spontaneous self-elimination reaction which eventually breaks down the polymer into smaller molecular weight species [Scheme 1(a)].

CSPs derived from BHA undergo a double 1,4-elimination reactions [Scheme 1(a)] on each residue, leading to complete backbone degradation; however, even one of the two self-elimination reactions of the BHA would result in polymer backbone degradation. Thus, it is excessive to use the BHA for the design of the trigger responsive domain (TRD) of CSPs, as any benzyl alcohol can possibly be such a TRD as long as the TRD has the (4-aminophenyl)methanol structure [Scheme 1(b)]. Herein, we report the use of 2-nitrobenzyl (4-(1,2-dihydroxyethyl)phenyl) carbamate (1) and azalaic acid dichloride (2) for the design of the degradable poly(1/2) [Scheme 1(c)]. The resulting polymer undergoes a 1, 6-elimination reaction upon removal of the nitrobenzyl protecting group with UV irradiation. This polymer can be used for future applications and materials in microcapsule shells for self-healing applications and in environmentally responsive coatings whose wettability and adhesion change in response to a stimulus.

EXPERIMENTAL

Materials
All chemicals were purchased from Sigma-Aldrich (St. Louis, MO, USA) and used as received unless otherwise specified. Anhydrous dichloromethane (DCM) and tetrahydrofuran (THF) were dried by a column packed with alumina. Anhydrous dimethylformamide (DMF) was dried by passing the solvent through a column packed with 4Å molecular sieves.

Instrumentation
NMR spectra were recorded on a Varian U500, a VXR500 or on a U1500NB 500 MHz NMR spectrometer. High resolution
electrospray ionization mass spectrometry (HR-ESI-MS) experiments were conducted on a Waters Quattro II mass spectrometer. Size-exclusion chromatography experiments were performed on a system equipped with an isocratic pump (Model 1100, Agilent Technology, Santa Clara, CA, USA), a DAWN HELEOS multangle laser light scattering (MALLS) detector, and an Optilab rEX refractive index detector (Wyatt Technology, Santa Barbara, CA). The detection wavelength of HELEOS was set at 658 nm. Separations were performed using serially connected size exclusion columns (50, 100, 500, and 100 Å Phenogel columns, 5 μm, 300 × 7.8 mm, Phenomenex, Torrance, CA) at 60 °C using DMF containing 0.1 M LiBr as the mobile phase. The MALLS detector is calibrated using pure toluene with no need for calibration using polymer standards and can be used for the determination of the absolute molecular weights (MWs). The molecular weight of polymer was determined from the dn/dc value calculated offline by means of the internal calibration system processed by the ASTRA V software (Version 5.1.7.3, Wyatt Technology).

Scanning electron microscopy (SEM) images were collected using a Hitachi S-4800 SEM at an operating voltage of 15 kV. Particle size and dispersity were measured with a ZetaPlus dynamic light scattering detector (15 mW laser, incident beam at 676 nm, Brookhaven Instruments, Holtsville, NY). UV irradiation was performed using a high pressure mercury vapor short arc bulb from an Omnicure S1000 with the adjustable collimating adaptor. The beam irradiating the sample was at a power of 50 mW cm⁻². The probe sonication was performed using a probe sonicator (700 W, 20 kHz, Fisher Scientific, Pittsburgh, PA, USA). HPLC was performed on a Shimadzu HPLC system (LC-20AT) connected with PDA detector (SPD-M20A) and fluorescence detector (RF-20A). Shimadzu C18 column (3 μm, 50 × 4.6 mm² dimension) was used for analysis. The mobile phase consisted of 0.1% TFA/Water and acetonitrile with flow rate 1.5 mL/min. The UV wavelength for detecting pyrene derivatives was set at 343 nm. UV-vis absorption was recorded by Cary 5000 spectrophotometer from Agilent Technologies.

**SCHEME 1** Illustration of the degradation of 2, 6-bis(hydroxymethyl) aniline (BHA) (a) and 1-(4-aminophenyl) ethane-1,2-diol based polymers (b); (c) Synthesis of degradable poly(1/2) and chemical structure of control polyBoc.
Polymer Synthesis

**Synthesis of 2-Nitrobenzyl(4-vinylphenyl)carbamate**

2-Nitrobenzyl alcohol (0.92 g, 6 mmol) in 5 mL anhydrous THF was added to a stirred solution of phosgene (15 wt % in toluene, 9 mL, 12.6 mmol) in 10 mL anhydrous THF under nitrogen at 0 °C. The reaction was stirred for 6 h and then the solvent and excess phosgene was removed under vacuum. The resulting oil-like compound (1.29 g, 6 mmol) was then added to 10 mL THF at room temperature for 48 h. The crude product was obtained after removal of ethyl acetate. The product was purified by column chromatography (hexane: ethyl acetate = 2:1, v/v) to afford the product as a white solid. (1.0 g, yield 56%). 1H NMR (DMF-d<sub>6</sub>, 500 MHz): δ 9.97 (s, 1H, Ar−NH−CO−O−), 8.13 (d, 1H, ArH), 7.87–7.71 (m, 2H, ArH), 7.68–7.59 (m, 1H, ArH), 7.48–7.35 (m, 4H, ArH), 6.64 (d, 1H, −Ph−CH=CH<sub>2</sub>), 5.70 (d, 1H, −Ph−CH=CH<sub>2</sub>), 5.48 (s, 2H, Ph−CH<sub>2</sub>−O−CO−), 5.13 (d, 1H, −Ph−CH=CH<sub>2</sub>). 13C NMR (DMF-d<sub>6</sub>, 500 MHz): δ 153.5, 148.0, 139.2, 136.8, 134.9, 132.9, 132.3, 129.9, 127.4, 125.6, 118.9, 63.2. ESI-MS (low resolution, positive mode): calculated for C<sub>16</sub>H<sub>16</sub>N<sub>2</sub>O<sub>6</sub>Na 355.1, found 355.1 [M + H]<sup>+</sup>; calculated for C<sub>16</sub>H<sub>15</sub>N<sub>2</sub>O<sub>4</sub>Na 332.9, found 332.9 [M + Na]<sup>+</sup>

**Synthesis of 2-Nitrobenzyl(4,12-dihydroxyethyl)phenyl)carbamate (1)**

2-Nitrobenzyl (4-vinylphenyl)carbamate (1.0 g, 3.3 mmol) and K<sub>2</sub>OsO<sub>4</sub> (62 mg, 0.156 mmol) were dissolved in acetone/H<sub>2</sub>O (3:1, v/v, 100 mL), and then 4-methylmorpholine N-oxide (NMO) (586 mg, 5 mmol) was added. The mixture was stirred at room temperature overnight and saturated aqueous solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10 mL) was then added to quench the reaction. After 12 h, the resulting solution was purified by silica gel column chromatography (hexane: ethyl acetate = 1:1 to 0:1, v/v) to give compound 1 (0.87 g, yield 80%) as a white solid. 1H NMR (DMSO-d<sub>6</sub>, 500 MHz): δ 9.83 (s, 1H, Ar−NH−CO−O−), 8.13 (d, 1H, ArH), 7.81 (d, 1H, ArH), 7.76–7.71 (m, 2H, ArH), 7.66–7.58 (m, 1H, ArH), 7.38 (d, 2H, ArH), 7.26–7.19 (m, 2H, ArH), 5.47 (s, 2H, Ph−CH=CH<sub>2</sub>−O−CO), 5.12 (d, 1H, −CH=CH<sub>2</sub>−OH), 4.65 (t, 1H, −CH<sub>2</sub>−CH=CH<sub>2</sub>−OH), 4.49–4.42 (m, 1H, −CH<sub>2</sub>−O−CO), 3.40–3.34 (m, 2H, −CH<sub>2</sub>−CH=CH<sub>2</sub>−OH). 13C NMR (DMSO-d<sub>6</sub>, 500 MHz): δ 153.6, 147.9, 138.4, 138.1, 134.8, 133.0, 129.9, 127.3, 125.5, 118.5, 74.1, 68.1, 63.0. ESI-MS (low resolution, positive mode): calculated for C<sub>21</sub>H<sub>21</sub>N<sub>2</sub>O<sub>4</sub>Na 377.1, m/z; [M + Na]<sup>+</sup>; found 355.1 [M + Na]<sup>+</sup>

**Synthesis of Poly (1/2)**

To the solution of compound 1 (332 mg, 1 mmol) and azelaic acid dichloride (225 mg, 1 mmol) in DCM (3 mL), anhydrous pyridine (0.483 mL, 6 mmol) was added dropwise over 10 min under nitrogen. The solution was stirred for 22 h at room temperature. The reaction mixture was concentrated to 0.5 mL under vacuum, and precipitated into cold methanol (10 mL). The precipitate was collected by centrifugation at 4000 r.p.m. and dried under vacuum. Poly (1/2) was obtained as a light yellow solid (400 mg, yield 80%). M<sub>n</sub> = 11,200 g mol<sup>−1</sup>; M<sub>w</sub>/M<sub>n</sub> = 1.24. 1H NMR (CDCl<sub>3</sub>, 500 MHz): δ 8.09 (d, 1H, ArH), 7.67–7.21 (m, 7H, ArH), 5.95 (s, 1H, Ar−NH−CO−O−), 5.58 (d, 2H, Ph−CH=CH<sub>2</sub>−O−CO), 4.28 (s, 2H, −CH=CH<sub>2</sub>−O−CO), 3.65 (s, 1H, Ph−CH=CH<sub>2</sub>−), 2.35–2.23 (m, 4H, −CO−CH<sub>2</sub>−CH<sub>2</sub>−), 1.59–1.19 (m, 10H, −OCO−CH<sub>2</sub>−(CH<sub>2</sub>)<sub>3</sub>−CH<sub>2</sub>−).

General Procedure for the Photolysis of Poly(1/2) or PolyBoc and Analysis of the MWs by GPC

A DMF/H<sub>2</sub>O (95:5, v/v) solution (1 mL) of poly (1/2) or polyBoc (10 mg/mL) in a quartz cuvette was placed under illumination from the UV source (365 nm, 50 mW cm<sup>−2</sup>) and irradiated for 40 min or 2 h. The resulting solution was then incubated under dark at 37 °C for 96 h before it was dried under vacuum. The residue was dissolved in DMF (1 mL) and used for the MW analysis by GPC.

General Procedure for Analysis of Degradation Kinetics of 3 by 1H NMR

The solution of 3 in DMSO-d<sub>6</sub>: D<sub>2</sub>O (5:1, v/v, 1.3 mM) in a quartz cuvette was placed inside a photoreactor and irradiated by UV light (365 nm, 50 mW cm<sup>−2</sup>) for different time (0, 40 min, 80 min) and then the resulted solution was incubated at 37 °C for different period of time. The solution was used for the degradation analysis of 3 by 1H NMR.

General Procedure for Analysis of Degradation Species of 3 by HPLC

A CH<sub>3</sub>CN/H<sub>2</sub>O (9:1, v/v) solution of 3 (0.2 mg mL<sup>−1</sup>) in a quartz cuvette was placed under illumination from the UV source (365 nm, 50 mW cm<sup>−2</sup>) and irradiated for 1 h. The resulting solution was incubated at 37 °C under dark. At different time point (0, 22, 44, 66, and 90 h), a small aliquot of the solution (250 μL) was diluted with 500 μL CH<sub>3</sub>CN and 100 μL DMF before analysis by HPLC. F2 peak was confirmed by ESI (high resolution mode; calculated for C<sub>16</sub>H<sub>16</sub>N<sub>2</sub>O<sub>5</sub>Na 694.2964, m/z, [M + H]<sup>+</sup>; found 694.2957 [M + H]<sup>+</sup>) and F5 peak was confirmed by comparison with standard.

General Procedure for the Preparation of Nile Red Encapsulated Polymer (1/2) Based Nanoparticles and UV-Triggered Release of Nile Red from the Nanoparticles

Poly (1/2) (20 mg) and Nile Red (0.5 mg) were dissolved in DCM (2 mL), and the solution was added to DI-water (40 mL) containing 1% PVA (vinalcohol) (PVA). The mixture was stirred at 1000 rpm for 10 min. The above mixture was sonicated by probe sonication for 5 min (40 W, 1 s pulse with 1 s delay) under ice bath. The suspension was further stirred at 500 rpm using a magnetic stirrer to evaporate DCM overnight. The nanoparticles were collected by ultracentrifugation at 12 000 rpm for 20 min and washed twice with water to remove PVA and dried by lyophilization. An aqueous solution of Nile Red loaded nanoparticles of poly (1/2) (50 μg mL<sup>−1</sup>) in a quartz cuvette was irradiated at 50 mW cm<sup>−2</sup> for a specific period of time. The resulting solution was used for fluorescence analysis (λ<sub>ex</sub> = 556 nm; λ<sub>em</sub> = 634 nm). Known amount of Nile Red loaded...
results of our model compound (see below) and previous studies on self-immolative linkers based degradable polymers.\textsuperscript{27,28} The solvent was then removed under vacuum followed by dissolution of the residue in DMF. The changes in polymer molecular weights (MWs) were then monitored using GPC. As shown in Figure 1(b), the MWs of UV-irradiated samples for 40 and 120 min were 9050 and 6690 g mol\textsuperscript{-1}, corresponding to 19 and 40\% reduction of their original MWs, respectively. UV light induced degradation of poly(1/2) was also confirmed by \textsuperscript{1}H NMR spectrum of poly(1/2) in DMSO-\textit{d}_6/\textit{D}_2O (10:1, v/v) (365 nm, 50 mW cm\textsuperscript{-2}) after the UV treatment for 40 min and followed by incubation at 37 °C for 96 h (Supporting Information Fig. S1). In a control experiment, we irradiated the polymer solution of polyBoc for 120 min with UV light and incubated the resulting solution at 37 °C for 96 h. As shown by the GPC trace in Supporting Information Figure S2(a), no remarkable change of molecular weight was observed. Moreover, after incubation of the solution of poly(1/2) in the same conditions in the dark for one week, the molecular weight of the polymer remained unchanged [Supporting Information Fig. S2(b)]. Taken together, these data indicate that polymer backbone fragmentation is controlled exclusively by the removal of the triggering groups through UV light and that no side reactions such as hydrolysis occurred during the long UV irradiation time or dark incubation time.

The degradation of poly(1/2) likely occurs by means of a 1,6-elimination at deprotected repeating unit [Fig. 1(a)].\textsuperscript{23,36} The degradation starts when the aniline moiety [A, Fig. 1(a)] is unmasked by cleavage of the protecting group (P) to form A1, which then undergoes spontaneous 1,6-elimination reaction to cleave the ester at the benzylic position and form a reactive azaquinone-methide intermediate (A2). Intermediate A2 is then trapped by H\textsubscript{2}O to form A3. Ideally, when the P group is removed from all the repeating units, the resulting P-depleted polymer (A1) becomes unstable and shatters to A4.
To confirm this degradation mechanism, we prepared 3 [Fig. 2(a)], a small-molecule analogue containing the triggering structure of the poly(1/2) but with an easily detectable pyrene moiety via the reaction of TRD 1 and 1-pyrenebutyric chloride [SI, Scheme S2]. Analysis of a solution of 3 in DMSO-d$_6$/D$_2$O (5:1, v/v) by LC-MS after UV irradiation (365 nm, 50 mW cm$^{-2}$) for 2 h showed F4, F5, and F6 were the major degradation products, suggesting the desired degradation occurred at the majority of repeating unit sites. Interestingly both the nitrosobenzaldehyde (F1) was observed, along with the detection of small amounts of the unstable species F2. In our previous work with the BHA, we did not observe the aniline intermediate after UV irradiation. The discrepancy suggests that 1,6-elimination reaction mentioned herein to form F4 is not as fast as the 1,4-elimination reaction in CSPs prepared with BHA [Scheme 1(a)]. As such, it is not surprising that a small peak of F3 was also detected because of trapping F2 by F1 before its 1,6-elimination to form F4.

We then investigated the degradation kinetics of 3 by monitoring the released percentage of final fragments via $^1$H NMR spectrum in DMSO-d$_6$/D$_2$O (5:1, v/v) by LC-MS after UV irradiation (365 nm, 50 mW cm$^{-2}$) for 2 h showed F4, F5, and F6 were the major degradation products, suggesting the desired degradation occurred at the majority of repeating unit sites. Interestingly both the nitrosobenzaldehyde (F1) was observed, along with the detection of small amounts of the unstable species F2. In our previous work with the BHA, we did not observe the aniline intermediate after UV irradiation. The discrepancy suggests that 1,6-elimination reaction mentioned herein to form F4 is not as fast as the 1,4-elimination reaction in CSPs prepared with BHA [Scheme 1(a)]. As such, it is not surprising that a small peak of F3 was also detected because of trapping F2 by F1 before its 1,6-elimination to form F4.

We then investigated the degradation kinetics of 3 by monitoring the released percentage of final fragments via $^1$H NMR spectrum in DMSO-d$_6$/D$_2$O (5:1, v/v). A solution of 3 was irradiated with UV light for 40 and 80 min, respectively, and then incubated at 37 °C at dark. $^1$H NMR analysis of the resulting solution was recorded at appropriate time intervals. Figure 3(b) reveals the spectrum of 3 after UV irradiation for 80 min following incubation under dark for 80 h. To identify the major peaks, we synthesized 2-hydroxy-2-phenylethyl octanoate (4) for comparison (Supporting Information Scheme S3 and Fig. S3) and its structure was confirmed by gHMBC and mass spectrometry. F5 is chosen as the target molecule since it is the final degradation fragment and its peak assignments can be exclusively identified by

FIGURE 2 (a) Proposed degradation mechanism of 3 upon exposure to UV treatment; (b) LC-MS analysis of degradation fragments of 3 after UV treatment (365 nm, 50 mW cm$^{-2}$, 2 h).
taking the $^1$H NMR spectrum of standard F5 [Fig 3(c)]. After UV light irradiation (365 nm, 50 mW cm$^{-2}$) for 80 min, the integration of peak l (5.41 ppm) decreased to 25%, which means 75% of the nitrobenzyl group was removed after UV light irradiation [Supporting Information Fig. S4]. At the same time, a new peak e$'$ (3.31 ppm) assigned to F5 appeared whose integration increased with incubation time. The percentage of released F5 was calculated by the integration of peak e$'$ versus the total integration of peak f and peak f. (Supporting Information). As a comparison, without any treatment, 3 showed no hydrolysis in one month as demonstrated by unchanged $^1$H NMR spectra (Supporting Information Fig. S5), revealing the release of F5 was due to the cleavage of protecting group. Figure 4 shows the release profile of F5 with incubation time after UV irradiation. After about 90 h, target molecule F5 was released to reach its saturated concentration. As we expected, 75% of F5 was released from 3 when 75% of protecting group was removed. In the case where UV irradiation was carried out for 40 min, 45% of the nitrobenzyl group was cleaved and after about 90 h postreaction incubation in the dark, the amount of F5 released was also found to 45% in the final solution. The half-life of 1,6-elimination reaction in our study is thus close to 40 h.

It should be mentioned that typical reaction-rate of 1,6-elimination using 4-aminobenzyl alcohol as a spacer is fast and typically the substrate is able to be fully released within 1 - 2 h after de-masking the protecting group in aqueous solution. The unexpected slow degradation kinetics of 3 likely arises from the effect of –CH$_2$OCO- substitution at the benzylic methylene position. It has been reported that electron donating substituents, such as a methyl group, increase the elimination rate and it is expected that electron withdrawing effects of the ester group in our work have the opposite effect, leading to prolonged lifetime of the deprotected aniline moiety (F2). To confirm our hypothesis, time course monitoring presence of the key intermediate (F2) and final product (F5) was conducted by HPLC as shown in Figure 5 and Supporting Information Figure S6. As expected, F2 showed corresponding opposite change trend as F5 indicating the substantial elongated lifetime of the
intermediates. This result may imply that different rates of 1, 6-elimination can be achieved by tuning the substituents at the benzylic methylene position.

We then explored the use of the trigger-responsive poly(1/2) for controlled release applications. We first attempted to control the release of the dye Nile Red from nanoparticles (NPs) prepared from the poly(1/2). NPs encapsulating Nile Red with 1.4% content were prepared from poly(1/2) by means of conventional emulsion methods due to the negligible solubility of poly(1/2) in water. The average diameter of the NPs was 351 nm ± 150, as determined by dynamic light scattering (DLS) and confirmed by SEM [Fig. 6(a,b)]. The release of the Nile Red payload from poly(1/2) NPs upon UV treatment was detected by fluorescence spectroscopy. As shown in Figure 6(c) and Supporting Information Figure S7, the fluorescence intensity decreased by 74%, showing the burst release of Nile Red from poly(1/2) based nanoparticles after UV treatment for 30 seconds. In a control study, the suspension of NPs without UV irradiation showed no dramatic change of fluorescence intensity over one week (Supporting Information Fig. S8). The fluorescence intensity dropped quickly, indicating the trigger-induced burst release of Nile Red from the NPs into a more polar environment (water) from hydrophobic NPs as reported in previous literature.\(^{27,28}\)

**CONCLUSIONS**

In summary, we developed 1-(4-aminophenyl)ethane-1,2-diol based polymer (poly(1/2)) that could be degraded upon trigger-induced removal of the aniline protecting groups [Scheme 1(b)]. The degradation of these polymers contrasts with that of self-immolative polymers, which depolymerize sequentially from one chain end to the other. We used poly(1/2) to prepare dye-containing NPs from which the encapsulated molecules could be rapidly released upon trigger-induced degradation. This study revealed the feasibility of making stimuli-responsive polymer by utilizing the derivative of 1,4-aminobenzyl alcohol and its application as delivery vehicles. Since the protecting group of 1,4-aminobenzyl alcohol can be tuned easily and the degradation kinetics of such derivatives might be controlled by choosing different substituent groups on the benzylic methylene position, this strategy may be a promising way to prepare stimuli-responsive system owning both “on-demand” responsiveness and controlled degradation rate. Such programmable responsive system may have many potential applications as microcapsule shell materials that release healing reagents for self-repairing purpose\(^{12,41,42}\) and in smart surface coatings that change wettability in response to environment.\(^{43}\)

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