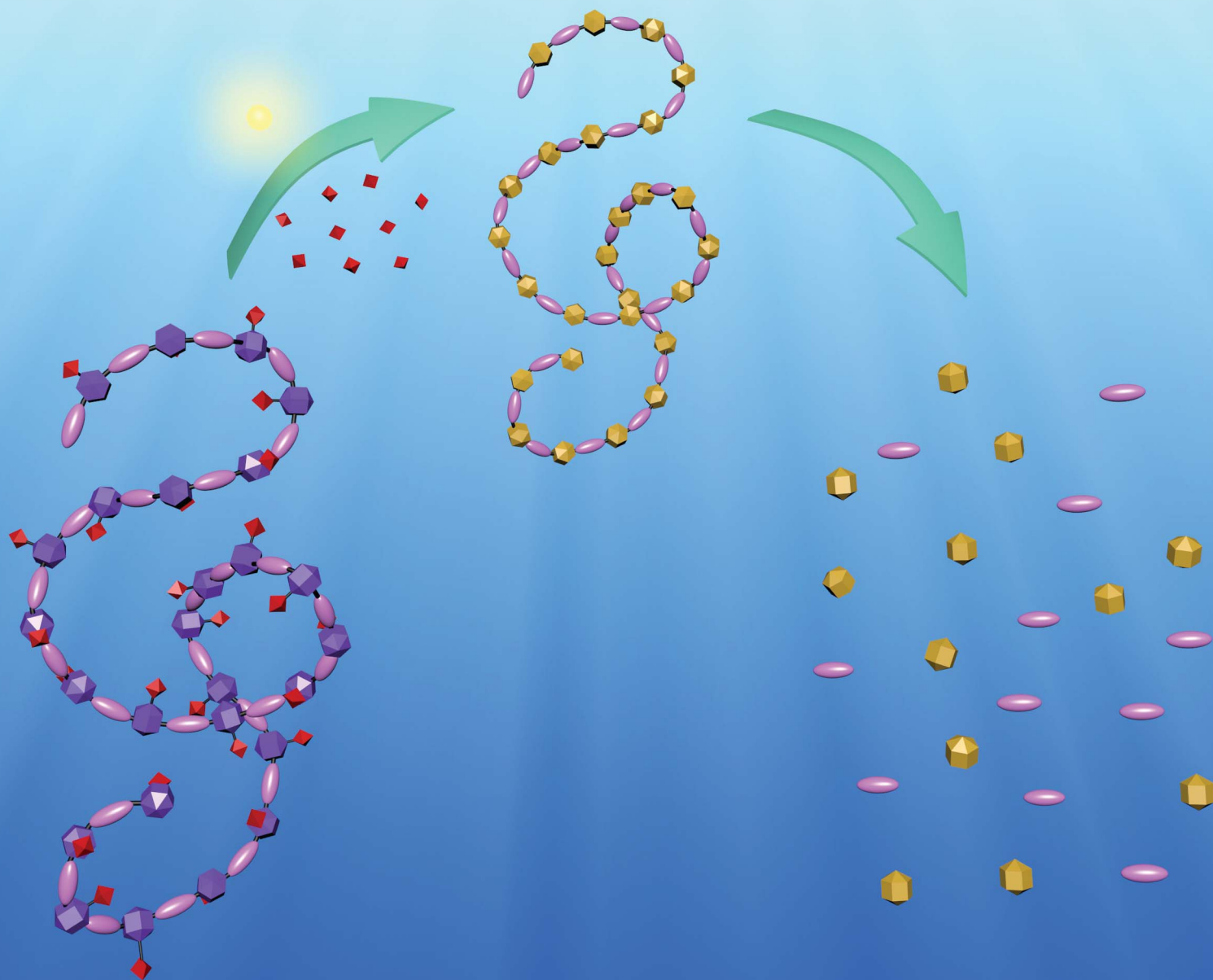


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Trigger-responsive chain-shattering polymers



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Trigger-responsive chain-shattering polymer†

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We designed 2,6-bis(hydroxymethyl)anilines bearing protecting groups sensitive to UV light, acid, or base, and used the protected anilines as co-monomers for the synthesis of trigger-responsive polymers. The resulting polymers underwent chain-shattering degradation once the protecting groups were removed, which could be used for trigger-responsive burst release applications.

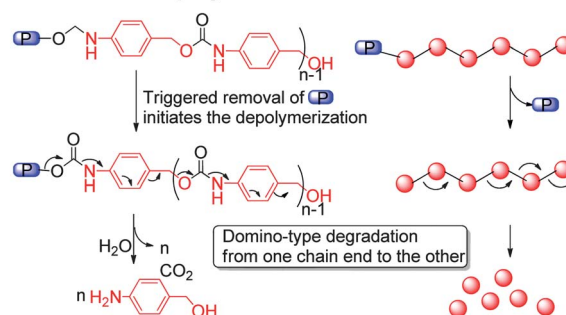
Introduction

Smart polymers that are stable under ambient conditions but degrade rapidly in response to external triggers have attracted interest because they are synthetically challenging and have broad utility.^{1–11} Various triggers such as light,^{12–20} changes in pH^{21–34} and temperature,^{35,36} enzymes,^{37–40} redox agents,^{41–48} and ultrasound^{49,50} can be exploited in the design of such smart materials.^{51–58} Self-immolative polymers, a class of trigger-responsive materials, have received much attention recently because their degradation can be precisely controlled.^{41,59–67} Aniline derivatives with a methylalcohol substituent in the *para* or *ortho* position are key building blocks for such polymers (Scheme 1a); the aniline monomers self-condense to form polymers with a urethane backbone and a terminal amine protected by a trigger-responsive protecting group. Once the removal of the protecting group is triggered, degradation by means of a 1,6- or 1,4-elimination reaction is initiated from one chain end and propagates spontaneously through the polymer backbone to the other end. The process is driven by the release of CO₂ and leads to the complete degradation of the backbone.

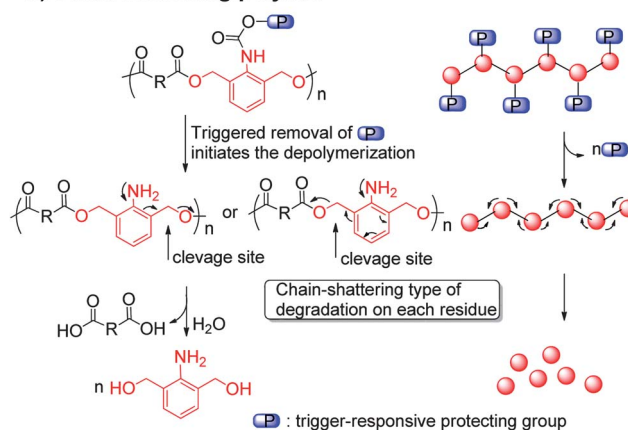
In this study, we redesigned self-immolative polymers, aiming to construct polymers that would undergo degradation only at the triggered sites. We reasoned that if we constructed a polymer from a 2,6-bis(hydroxymethyl)aniline (BHA) building block (Scheme 1b), with the two hydroxyl groups forming the polymer backbone and

the protected pendant amine serving as a trigger-responsive group, application of the trigger to remove the protecting groups would result in elimination reactions at each repeating unit. Thus, depolymerization would proceed by means of a chain-shattering mechanism rather than by the propagated, stepwise mechanism observed for self-immolative polymers from one chain end to the other (compare Scheme 1a and b). By varying the co-monomer structure (R in Scheme 1b), we would be able to generate a large

a) Self-immolative polymer



b) Chain-shattering polymer



P: trigger-responsive protecting group

Scheme 1 (a) Self-immolative polymer and (b) chain-shattering polymer.

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variety of chain-shattering polymers (CSPs) with responsiveness similar to self-immolative polymers. The CSPs reported in this paper are structurally closely related to condensation polymers developed by Almutairi *et al.*^{68–71} and Zhao *et al.*,^{72,73} further expanding the library of smart polymers that could undergo spontaneous depolymerization in response to external triggers.

Results and discussion

Design of CSPs

To demonstrate the concept, we synthesized BHA derivatives **1a–c**, which have photolabile *o*-nitrobenzyloxycarbonyl, acid-labile *tert*-butyloxycarbonyl, and base-labile 9-fluorenylmethoxy-carbonyl protecting groups, respectively (Scheme 2). Condensation polymerization of **1a–c** with hexamethylene diisocyanate (**2**) or azelaic acid dichloride (**3**) yielded polymers with urethane (poly(**1/2**)) or ester backbones (poly(**1/3**)), respectively. The number average molecular weights (MWs, M_n) of the polymers ranged from 6.9 to 15.6 kDa, and the molecular weight distributions (MWDs) were around 1.5, which is typical for condensation polymers (entries 1–4, Table 1). For control experiments, we used 1,3-benzenedimethanol (**4**) to prepare poly(**4/2**) ($M_n = 4.0$ kDa, MWD = 1.30) and poly(**4/3**) ($M_n = 9.3$ kDa, MWD = 1.58), the corresponding polymers without the trigger-responsive groups (Scheme 2; entries 5 and 6, Table 1).

We next evaluated the stability of the polymers under various triggering conditions, and we followed the change of their MWs by gel permeation chromatography (GPC). When the control polyurethane (poly(**4/2**)) or polyester (poly(**4/3**)) was treated with 1 : 1 (v/v) trifluoroacetic acid (TFA)–dichloromethane for 10 h, piperidine (20%) in dimethylformamide for 10 h, or UV light (365 nm, 40 mW cm^{-2}) for 1 h, there was no noticeable change in the MW or MWD of the polymers (entries 7–10, Table 1; Fig. 1a). However, when poly(**1a/2**) was exposed to UV light, it exhibited the expected UV responsiveness, and its MW decreased drastically with prolonged treatment (Fig. 1b; compare entries 11 and 12 to entry 1, Table 1). For example, the MW of poly(**1a/2**) decreased from 6.9 kDa (entry 1, Table 1) to 1.8 kDa (entry 12, Table 1) after UV treatment for 2 h. The UV-triggered degradation of poly(**1a/3**) was much faster than the degradation of poly(**1a/2**): the MW of the former decreased to 1/7 of its original value (from 13.8 to 1.9 kDa) after UV treatment for only 0.5 h (compare entries 2 and 14, Table 1). Poly(**1b/2**) and poly(**1c/2**),

Table 1 Degradation of chain-shattering polymers with or without UV light, acid, or base treatment

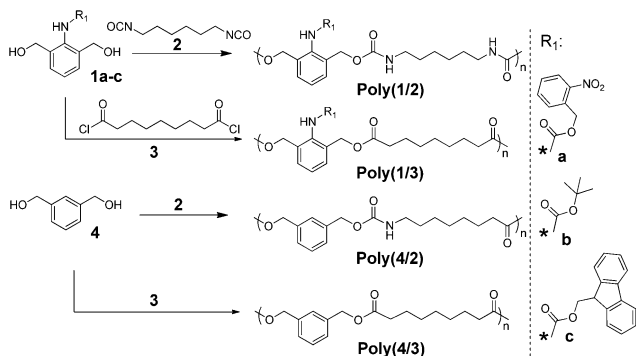
Entry	Polymer	Triggering condition ^a	Time (h)	M_n (kDa) ^b	MWD
1	Poly(1a/2)	—	—	6.9	1.48
2	Poly(1a/3)	—	—	13.8	1.46
3	Poly(1b/2)	—	—	10.9	1.36
4	Poly(1c/2)	—	—	15.6	1.56
5	Poly(4/2)	—	—	4.0	1.30
6	Poly(4/3)	—	—	9.3	1.58
7	Poly(4/2)	UV	1	3.9	1.31
8	Poly(4/2)	TFA	10	4.1	1.30
9	Poly(4/2)	Piperidine	10	4.0	1.31
10	Poly(4/3)	UV	1	9.2	1.58
11	Poly(1a/2)	UV	1	2.8	2.68
12	Poly(1a/2)	UV	2	1.8	3.26
13	Poly(1a/3)	UV	0.2	7.5	2.35
14	Poly(1a/3)	UV	0.5	1.9	2.86
15	Poly(1b/2)	TFA	8	7.7	1.59
16	Poly(1c/2)	Piperidine	6	7.3	2.65

^a UV treatment (365 nm, 40 mW cm^{-2}), acid treatment (TFA– CH_2Cl_2 (1 : 1, v/v)), or base treatment (piperidine–dimethylformamide solution (1 : 4, v/v)). ^b Determined by gel permeation chromatography.

which have acid- and base-labile protecting groups, respectively, also underwent the corresponding acid- and base-induced degradation (entries 15 and 16, Table 1). The MWDs of all the degraded polymers (entries 11–16, Table 1) were much broader than the MWDs of their parental polymers (entries 1–4, Table 1).

Degradation of CSPs

The chain-shattering degradation likely occurs by means of a 1,4-elimination followed by a second 1,8-elimination at each deprotected repeating unit as shown in Scheme 3. The degradation starts when the aniline moiety (**A**) is unmasked by cleavage of the protecting group (R_1) to form **A1**. **A1** then undergoes spontaneous 1,4-elimination to cleave one ester or urethane bond and forms a reactive azaquinone-methide intermediate (**A2**). Intermediate **A2** is rapidly trapped by H_2O to form another unstable polymeric intermediate terminated by a monobenzylalcohol-substituted aniline (**A3**), which subsequently undergoes a second 1,8-elimination (**A3** → **A4**) to cleave the second ester or urethane bond of the repeating unit to form BHA. Thus, when the R_1 group is removed



Scheme 2 Synthesis of CSPs from trigger-responsive 2,6-bis(hydroxymethyl)anilines **1a–c** and nonresponsive 1,3-benzenedimethanol (**4**).

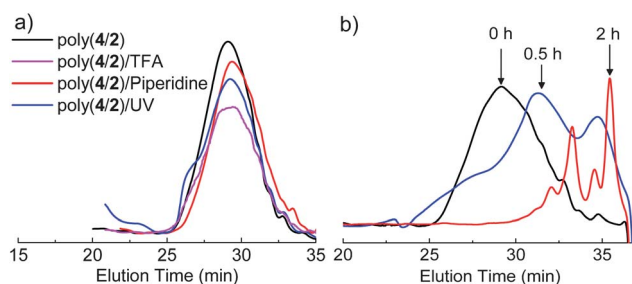
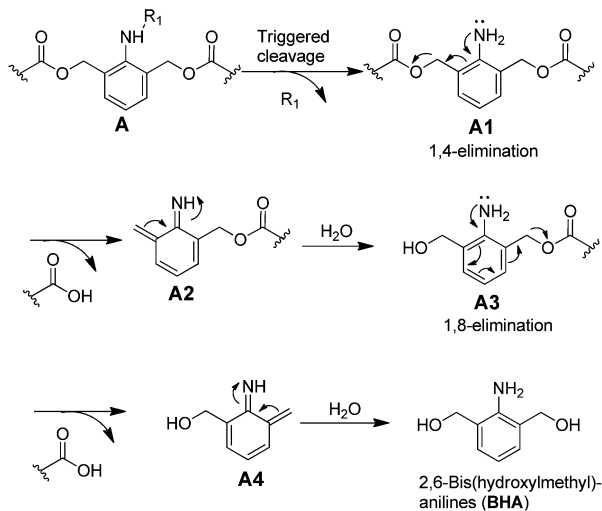


Fig. 1 Gel permeation chromatography curves of (a) poly(**4/2**) before and after treatment with TFA (10 h), piperidine (20% dimethylformamide solution, 10 h), or UV light (365 nm, 40 mW cm^{-2} , 1 h) and (b) poly(**1a/2**) before and after UV treatment (365 nm, 40 mW cm^{-2}).



Scheme 3 Proposed degradation mechanism of a CSP.

from all the repeating units, the resulting R_1 -depleted polymer (**A1**) becomes unstable and shatters to regenerate the monomer, as illustrated in Scheme 1b.

Degradation mechanism of CSPs

To confirm this degradation mechanism, we prepared **5** (Fig. 2), a small-molecule analogue containing the triggering structure of the CSPs but with an easily detectable pyrene moiety (R_2) prepared from **1a** and 1-pyrenebutyric chloride (Scheme S2 and Fig. S13[†]). Analysis of a solution of **5** in acetonitrile–water (9 : 1, v/v) by LC-MS after UV treatment for 45 min indicated that 1-pyrenebutyric acid (PBA) was the major degradation product (>90% yield; Fig. 2 and S14[†]). Except

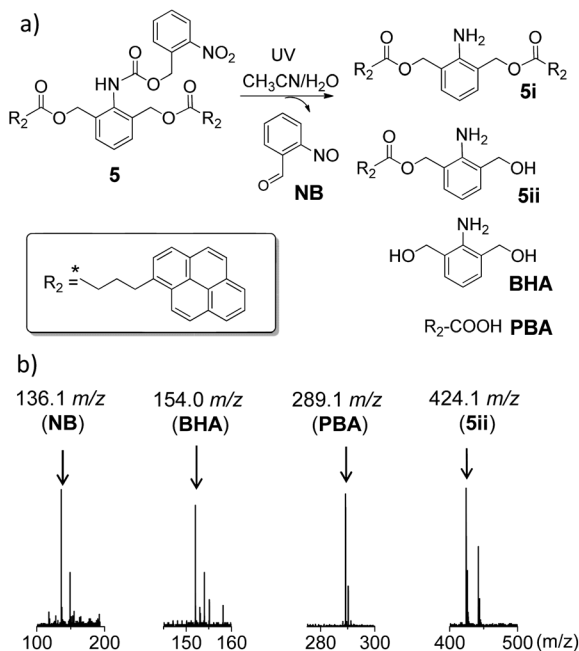


Fig. 2 (a) UV-triggered degradation of **5** and (b) LC-MS analysis of degradation fragments.

for intermediate **5i**, which may have been very unstable in the degradation solution, we detected all the other expected fragments resulting from degradation of **5** by means of the proposed chain-shattering mechanism (Scheme 3), including the unstable species nitrosobenzaldehyde (NB) and **5ii** (Fig. 2b).

Application of CSPs

We next explored the use of the trigger-responsive CSPs for controlled release applications. We first attempted to control the release of the dye Nile Red from nanoparticles (NPs) prepared from the CSPs. NPs encapsulating Nile Red were prepared from poly(**1a/3**) by means of conventional emulsion methods. The particle size was determined to be 290 nm by a dynamic light scattering technique (Fig. S15[†]). The release of the Nile Red payload upon UV treatment was detected by fluorescence spectroscopy. After UV treatment of the NPs in water for just 60 s (365 nm , 40 mW cm^{-2}), the fluorescence intensity dropped by 50% (Fig. 3a), indicating the trigger-induced burst release of Nile Red from the NPs into a more polar environment (water).^{68,72} In the absence of UV treatment, only a slight decrease in the Nile Red fluorescence intensity was observed, presumably due to the release of Nile Red by means of diffusion (Fig. 3a). The diameter of the NPs decreased from 290 to 230 nm after UV treatment for 10 min, whereas only a slight change in the particle diameter was observed in the absence of UV treatment (Fig. S16[†]).

We then attempted to trigger the controlled release of a small molecule from NPs prepared from the CSPs. NPs encapsulating camptothecin (CPT, used as a model drug here) were prepared from poly(**1a/3**) and poly(**4/3**) by means of a nanoprecipitation method with PEG-*b*-poly(L-lactide) as the stabilizing agent (CSP : PEG-*b*-poly(L-lactide) = 1 : 1, w/w).^{74–76} The release of the CPT payload was monitored by means of HPLC. After UV treatment for 30 min (365 nm , 20 mW cm^{-2}), 45% of the CPT was released from the poly(**1a/3**) NPs, whereas only 5% of the CPT was released (by means of diffusion) from the same NPs in the absence of treatment. The nearly 9-fold increase in the proportion of CPT released from the UV-irradiated NPs demonstrates the remarkable control of CPT burst release by means of trigger-induced chain-shattering degradation of polymers. For CPT-containing NPs prepared with control polymer poly(**4/3**), there was essentially no difference between the proportions of CPT released with and without UV treatment (Fig. 3b)

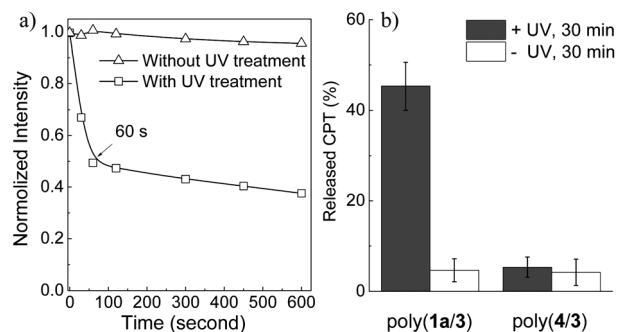


Fig. 3 (a) Normalized fluorescence intensity of Nile Red ($\lambda_{\text{Ex}} = 556\text{ nm}$, $\lambda_{\text{Em}} = 634\text{ nm}$) encapsulated in poly(**1a/3**) NPs before and after UV treatment (365 nm , 40 mW cm^{-2}). (b) Release of CPT from poly(**1a/3**) and poly(**4/3**) NPs irradiated for 30 min or unirradiated NPs (in phosphate buffered saline, 365 nm , 20 mW cm^{-2}).

and S17†). The CPT release kinetics from poly(4/3) NPs were similar to the release kinetics from poly(1a/3) NPs without UV treatment, further substantiating that the 9-fold increase in CPT release from the UV-irradiated poly(1a/3) NPs was due to UV-induced degradation of poly(1a/3).

Conclusions

In summary, we developed a class of 2,6-bis(hydroxymethyl)aniline-based polymers that underwent chain-shattering degradation simultaneously at each repeating unit upon trigger-induced removal of protecting groups (Scheme 1b). The degradation of these polymers contrasts with that of self-immolative polymers, which depolymerize sequentially from one chain end to the other (Scheme 1a). The CSPs rapidly degraded in response to various external triggers (UV light, acid, and base). We used the CSPs to prepare dye- and drug-containing NPs from which the encapsulated molecules could be rapidly released upon trigger-induced degradation. Given the remarkable control over degradation and burst release, we expect CSPs to be useful in controlled burst release applications.

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