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Multiresponsive Azobenzene End-Cap for Self-Immolative Polymers

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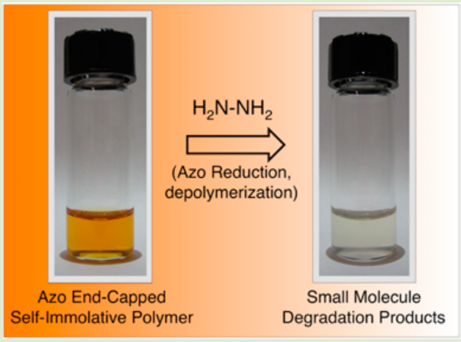
Supporting Information

ABSTRACT: Azobenzene was introduced as a new multiresponsive end-cap for self-immolative polymers. Using small-molecule model compounds, it was demonstrated that reducing agents including hydrazine and dithiothreitol could reduce the azobenzene to the corresponding hydrazobenzene, resulting in a 1,6-elimination reaction with the potential to initiate the depolymerization of self-immolative polycarbamates. An activated azobenzene derivative was then prepared, allowing for its incorporation as an end-cap for polycarbamates based on alternating *N*,*N*′-dimethylethylene diamine and 4-hydroxybenzyl alcohol. Upon treatment with hydrazine, depolymerization proceeded. To demonstrate the versatility of this end-cap, the chemistry was also applied to polycarbamates based on 4-aminobenzyl alcohol. In addition to allowing triggered depolymerization, the azobenzene end-cap also provides a visual signal upon triggering owing to the strong visible absorption of the azobenzene, which shifts to the UV range upon reduction. Furthermore, azobenzene is capable of undergoing *trans*—*cis* isomerization in response to UV light, providing multiple functions in a single end-cap.



Self-immolative linear polymers are a class of polymers that undergo end-to-end depolymerization in response to the cleavage of an end-cap from the polymer terminus. Their unique features, including a predictable degradation time dependent on polymer length[1] and the ability to change the stimulus to which they respond by simply changing the end-cap, have made them attractive materials for a wide range of applications including sensors,[2,3] controlled release systems,[4−7] shape-changing plastics,[8] and self-powered microscale pumps.[9] Thus far, a variety of polymer backbones including polycarbamates,[2,3,6,10] poly(carbamate-thiocarbamate)s,[11] polyphthalaldehydes,[12−15] poly(benzyl ethers),[16] and most recently polyglyoxylates[17] have been developed. In addition, various end-cap cleavage triggers have been explored, including light,[4,5,17] pH,[6] reduction,[11] oxidation,[2] and enzymes.[3,18,19]

Here we show that an azobenzene moiety can be used as a multiresponsive end-cap for self-immolative polymers. Azobenzenes are well-known chromophores and photoresponsive units that undergo *trans*—*cis* isomerization in response to irradiation with UV light.[20] A recent report describing the use of azobenzene to prepare substituted hydrazines in the presence of sacrificial hydrazine as a reductant[21] suggests that azobenzenes also have the potential to serve as end-caps for self-immolative polymers because the hydrazobenzene derivative resulting from the reduction process contains an anilinic nitrogen, which can trigger the depolymerization of self-immolative polymers via a 1,6-elimination reaction (Figure 1). Unlike nearly all other examples of end-caps, complete destruction of the end-cap is not required to initiate the depolymerization, as the reduction process is reversible following cleavage. Furthermore, conversion of the azobenzene to the resulting hydrazobenzene results in a visual color change, providing an optical read-out of the triggering event.

The first step in demonstrating the utility of azobenzene as an end-cap was to demonstrate the proposed chemistry on a small-molecule model compound that could be easily studied by UV—visible and NMR spectroscopic methods. As shown in Scheme 1, ethyl-4-aminobenzoate was oxidized by oxone to produce ethyl-4-nitrosobenzoate **1**. The ethyl ester was incorporated to ultimately provide an electron-withdrawing group in the final end-cap to enhance the rate of reduction.[21] Reaction of **1** with 4-aminobenzyl alcohol provided the azobenzene derivative **2**, which was acetylated to provide the target model compound **3**.

As shown in Figure 2a, upon addition of excess hydrazine (60 mM) to a solution of **3** (0.03 mM) in methanol, a hypsochromic shift was observed as the λ_{max} at 330 nm was replaced by a new λ_{max} at 300 nm. This can be attributed to the loss of conjugation between the aryl rings. An isosbestic point was observed at 309 nm, suggesting clean conversion of **3** to a single absorbing species over a period of 18 h. The large excess of hydrazine was required to generate an acceptable reaction rate under the dilute conditions of the UV—vis experiment. Figure 2b shows NMR spectra that provided confirmation of the conversion of **3** to **4** along with acetate (6 mM of **3** and 360 mM of hydrazine). Spectra of the products showed significant upfield shifts in the peaks corresponding to the benzylic and aromatic protons. The identity of **4** was confirmed through

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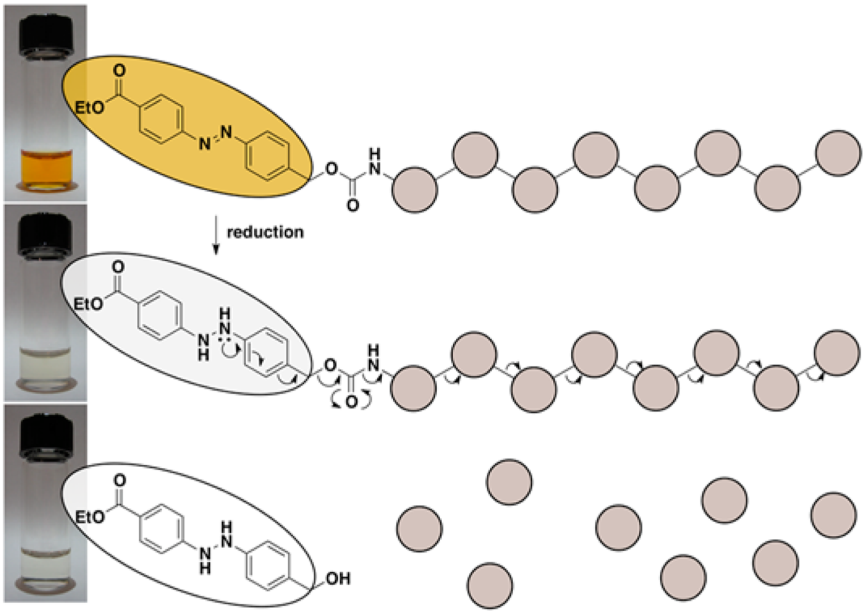
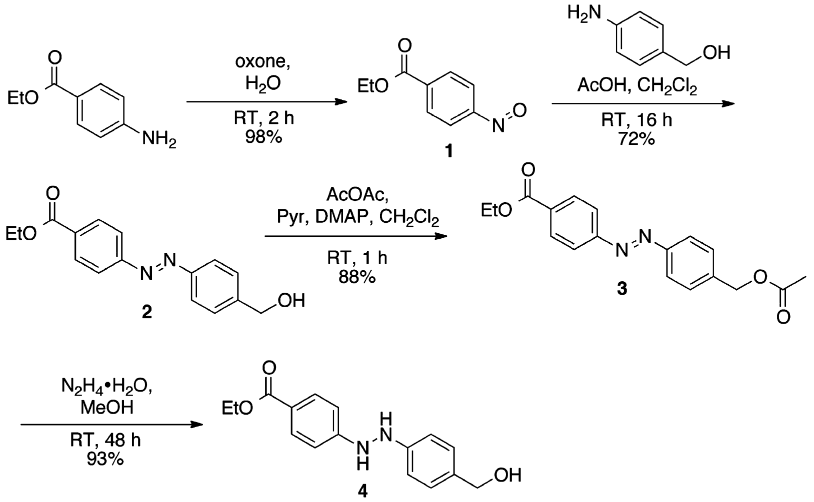


Figure 1. Schematic showing the color change and the initiation of depolymerization upon azobenzene reduction.

Scheme 1. Synthesis of an Azobenzene Model Compound



independent synthesis under similar conditions (Scheme 1), followed by full characterization. To confirm that the observed acetate came from the proposed 1,6-elimination reaction, control reactions were performed on both benzyl acetate and a benzyl carbamate derivative (as a model of the proposed carbamate end-cap from Figure 1). At the same hydrazine concentration used for the study of **3**, acetate generation was much slower for benzyl acetate, and no dimethylamine formation was observed for the carbamate (Figures S15−S17, Supporting Information). Combined, these results demonstrate that the proposed reductive/self-immolative mechanism is strongly dominant in comparison with possible nucleophilic or hydrolytic mechanisms.

While hydrazine is a specific chemical stimulus that may be useful in some applications, it was also of interest to demonstrate that the reduction of **3** is possible under biologically relevant conditions, as this would significantly expand the utility of the end-cap. Electrophilic diazenes such as diethyl azodicarboxylate are known to undergo reduction in the presence of free thiols.[22−24] More recently, acceleration of the thermal *cis*−*trans* isomerization of azobenzenes by thiols has been reported.[25] In addition, the reduction of azobenzenes by thiols has been observed as an undesirable side reaction in the application of azobenzenes in biological systems.[26,27] In our case, the reduction is desirable for initiation of depolymerization, so the reduction of **3** in the presence of dithiothreitol (DTT) was investigated. It was demonstrated by UV−visible and ^{1}H NMR spectroscopy that it was indeed possible to cleanly reduce compound **3** to compound **4** using DTT at millimolar concentrations (Figures S18 and S19, Supporting Information), providing this class of end-caps with an additional triggering stimulus that can potentially be applicable *in vivo* with a water-soluble system.

Having demonstrated the feasibility of cleanly reducing the model end-cap **3**, the next step was to introduce this moiety to the termini of self-immolative polymers. In one example, the azobenzene was incorporated as the end-cap for our previously reported self-immolative polycarbamate based on *N*,*N*′-dimethylethylene diamine and 4-hydroxybenzyl alcohol.[6] As shown in Scheme 2, this was accomplished by the conversion of

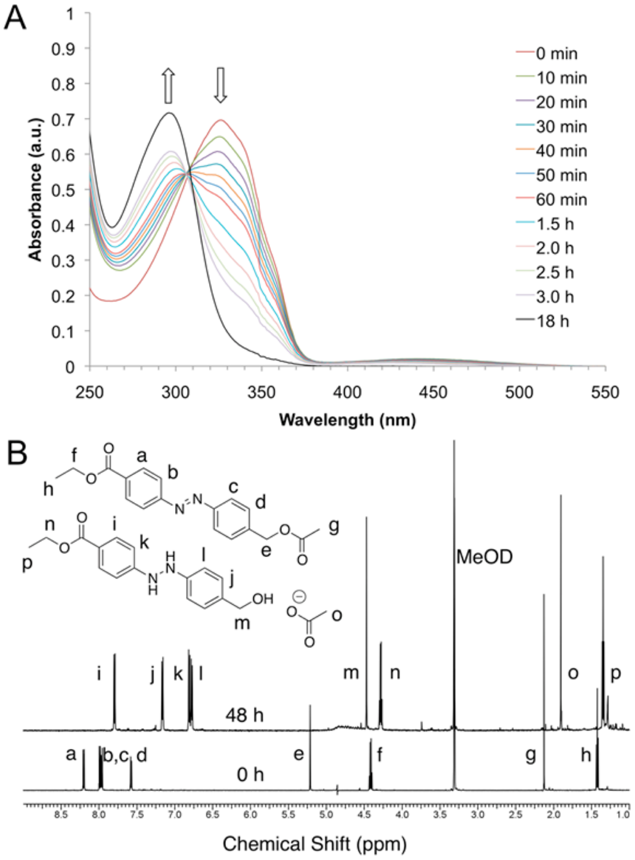
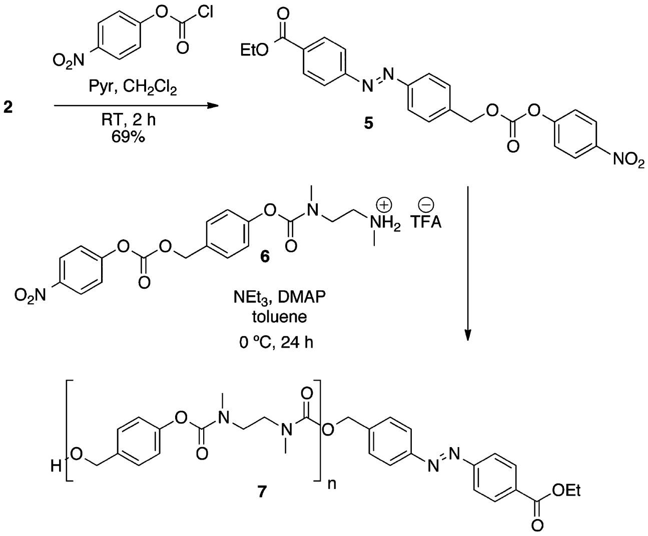


Figure 2. (A) UV−visible and (B) ^{1}H NMR spectra (600 MHz, CD_3OD) showing the conversion of **3** to the reduced product **4** with $N_2H_4{\cdot}H_2O$. A presaturation experiment was used to remove the H_2O signal in NMR.

Scheme 2. Synthesis of Azobenzene-Containing Polymer 7



2 into an activated carbonate by reaction with 4-nitrophenyl chloroformate to provide end-cap **5**. Polymerization using **5** with monomer **6**[6] in the presence of NEt_3 and 4-dimethylaminopyridine (DMAP) provided polycarbamate **7**. On the basis of size exclusion chromatography (SEC) relative to poly(methyl methacrylate) (PMMA) standards in DMF, this polymer had an M_W of 9200 g/mol and dispersity (Đ) of 1.6. UV−visible spectroscopy confirmed the presence of a strong end-cap absorbance at 330 nm in addition to the absorbance of the hydroxybenzyl alcohol-based polymer backbone at 270 nm.

The degradation of polymer **7** was studied in methanol. As shown in Figure 3a, upon the addition of hydrazine hydrate the azobenzene end-cap was reduced to the corresponding hydrazobenzene (λ_{max} = 300 nm), and the polymer solution changed from orange to colorless. The λ_{max} shifted to 278 nm, the absorption maximum of 4-hydroxybenzyl alcohol (Figure S21, Supporting Information), and became sharper and more intense, as the polymer degraded to 4-hydroxybenzyl alcohol and *N*,*N*′-dimethylimidazolidinone via a series of alternating 1,6-elimination-decarboxylation and cyclization reactions.[6] In NMR spectra, peaks corresponding to the expected depolymerization products 4-hydroxybenzyl alcohol and *N*,*N*′-dimethylimidazolidinone were observed to increase in intensity, while the corresponding polymer peaks decreased (Figure S22, Supporting Information). In addition, SEC showed complete polymer degradation with the exception of a small fraction of what is believed to be cyclic oligomers that cannot degrade (Figure S12, Supporting Information).[1,5,28] As shown in Figure 3b, in the absence of hydrazine, depolymerization was much slower. A *t*-butyloxycarbonyl (BOC)-end-capped control

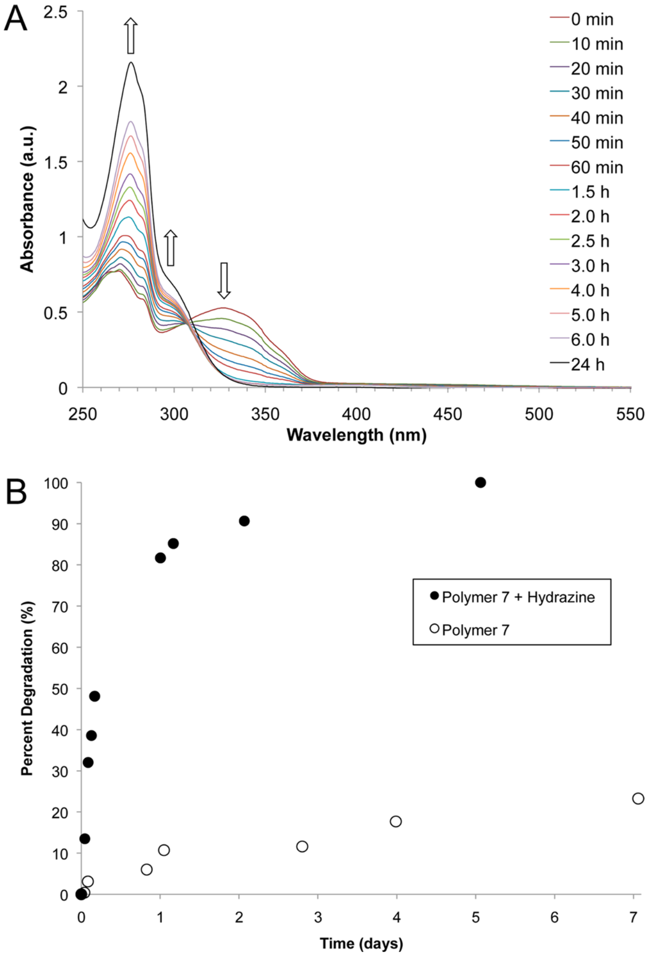
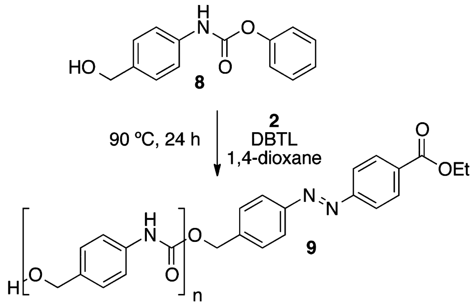


Figure 3. (a) UV−visible spectra obtained during the end-cap cleavage and depolymerization of **7** (∼0.09 mM) with hydrazine (360 mM) in CH_3OH. (b) Degradation of polymer **7** (∼1.8 mM) in the presence and absence of hydrazine (9 mM), as measured by ^{1}H NMR spectroscopy (600 MHz, CD_3OD).

polymer[6] was also studied in both the presence and absence of hydrazine. Its rate of depolymerization was very similar to that of polymer **7** in the absence of hydrazine, and the presence of hydrazine caused only a very small acceleration in the rate of depolymerization of this BOC-end-capped control (Figure S23, Supporting Information). Overall, this suggests that hydrazine does selectively reduce the azobenzene on the end-cap, leading to triggered depolymerization.

To demonstrate the versatility of the azobenzene end-cap, it was also incorporated into a polycarbamate based on 4-aminobenzyl alcohol, developed by Shabat and co-workers.[3] As shown in Scheme 3, monomer **8**[3] was polymerized in the presence of compound **2** as an end-cap using catalytic dibutyltin dilaurate (DBTL) in dry dioxane to provide polymer **9**. On the basis of ^{1}H NMR spectroscopy, the average chain length was ~6 units. The resulting material also appeared oligomeric by SEC, with a M_W of 3700 g/mol relative to PMMA and $Đ$ of 1.5. These results are consistent with the tendency of this polymerization to provide relatively short polymers.[2,3] In the current work, this provides the advantage of allowing the chemistry of the end-cap to be readily followed by spectroscopic methods.

Scheme 3. Conversion of Monomer 8 to Polymer 9



The degradation of polymer **9** was studied in DMF (Figures S25−S29, Supporting Information). Upon the addition of hydrazine the solution changed from orange to clear, providing a visual indication that the end-cap had been reduced and that polymer degradation could be initiated. Following this, depolymerization was followed by NMR spectroscopy, with 17% degradation observed over a period of 9 days at room temperature. This slow degradation rate was expected as the depolymerization of this particular class of self-immolative polymers is known to be slow under nonaqueous conditions.[10] In the absence of hydrazine, no degradation of polymer **9** was observed. Similarly, no degradation of a control polymer with an *n*-butyl end-cap was observed even in the presence of hydrazine (Figure S30, Supporting Information).

In addition to triggering the depolymerization of self-immolative polymers, azobenzenes are well-known to undergo *trans*−*cis* isomerization in response to irradiation with UV light. This process is of particular interest in the context of the reduction-sensitive moiety because recent studies have suggested an increased rate of reduction of the *cis* azobenzene relative to the *trans* isomer,[25] thus providing further control over the onset of degradation. Furthermore, the isomerization of azo-containing monomers in block copolymers has been studied,[29] wherein the polarity and morphology of the polymers were modified via irradiation. The single azobenzene hinge at the interface of two blocks may have the potential to provide a similar morphological disruption in an assembly, either via a change in the conformation or by modification of the polarity at the polymer interface. To confirm that the end-caps can also undergo this isomerization process orthogonally to their reduction, both model compound **3** and end-capped polymer **9** were irradiated with UV light (λ = 365 nm). After 30 min, more than half of the azobenzene moieties in each of these materials had converted from the *trans* conformation to the less stable *cis* conformation (Figures S31−S33, Supporting Information). After 24 h, they had both almost completely converted back to the *trans* conformation via thermal relaxation. Therefore, the azobenzene end-caps can respond in different ways to different stimuli, with reductive conditions leading to depolymerization and UV light leading to isomerization.

In conclusion, a novel azobenzene end-cap responsive to both reducing conditions and light was developed. This highly absorbant dye can act as a trigger for polymer degradation and as a reporter molecule due to its visual color change upon reduction. In addition, the azobenzene can undergo *trans*−*cis* isomerization in response to UV light without triggering other degradation processes. This isomerization, when incorporated for example between two blocks of copolymer, could effect changes in polymer assemblies or in the solid state and may also modulate the rate of reduction. Thus, this new multi-responsive end-cap opens new prospects for the application of self-immolative polymers in a wide range of stimuli-responsive materials.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, NMR spectra, SEC traces, additional data for the reduction, and *trans*−*cis* isomerization of the azobenzene in compounds **3**, **7**, and **9** control degradation studies. 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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