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Ultrasound-Induced Site-Specific Cleavage of Azo-Functionalized Poly(ethylene glycol)

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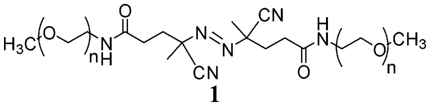
Polymers in solution undergo mechanical cleavage when exposed to ultrasound due to cavitation events.[1] The commonly accepted mechanism of chain scission involves the accumulation of stress on the polymer backbone due to solvodynamic shear. Specifically, when a polymer molecule is in the vicinity of a collapsing bubble, the end nearest to the cavitation site is pulled toward the cavity at a faster velocity than the far end. This velocity gradient causes the polymer molecule to elongate, setting up stresses along the backbone. Experimentally, the polymer chain has been found to rupture near its midpoint, where the solvodynamic forces are assumed to be the greatest.[1−4] The rate of polymer cleavage depends on a number of parameters including the frequency, intensity, and duration of ultrasound; the concentration, quality, temperature, vapor pressure, and gas solubility of the solution; and the composition of the polymer chain.[1,2] The rate of ultrasonic degradation is also directly proportional to polymer molecular weight for chains longer than a threshold value (typically 30 kDa).[1,2]

Encina and co-workers found that the rate of ultrasonic degradation of poly(vinylpyrrolidone) was 10 times faster when peroxy linkages were randomly incorporated into the polymer backbone.[5] This result was used to infer that ultrasonic degradation of a polymer occurs preferentially at weak bonds incorporated into the chain. However, no studies have been reported on well-defined link-functionalized polymers[6] in which the weak bond is positioned at a prescribed location. Here we show that mechanically induced cleavage can be localized almost exclusively to a single weak site when this reactive unit is positioned near the center of the polymer backbone. We also begin to address the question of how site-specific cleavage depends on the location of the single weak link in the polymer backbone.

An azo moiety was chosen as the cleavage site in the following experiments because the reaction pathway for thermal dissociation[7] should coincide with the bond angle and stretching deformations expected from the tensile forces caused by solvodynamic shear. Additionally, the energy of activation for the homolytic extrusion of nitrogen from the azo group is 24−30 kcal/mol,[7] about 2−3 times lower than that of the carbon−carbon bonds in the poly(ethylene glycol) backbone. Neradovic and coworkers synthesized link-functionalized polymer **1** consisting of 4,4′-azobis(4-cyanovaleric acid) flanked by poly(ethylene glycol) chains ($M_n = 500$ g mol^{-1});[8] their system was extended up to a total weight of 60 kDa for the following studies.



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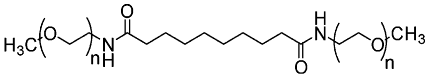
Demonstration of Site-Specific Cleavage. A 0.75 mg/mL solution of the azo-centered 40 kDa link functionalized polymer (**1**) was subjected to pulsed ultrasound (0.5 s on, 1.0 s off) at 20 kHz and 8.7 W/cm^2 in acetonitrile. Sonication was performed under argon, and the temperature was maintained at 6−9 °C where thermal decomposition[9] of the linker does not occur on a reasonable time scale. Aliquots were withdrawn at timed intervals, and polymer degradation was analyzed by GPC, using refractive index (RI) as the mode of detection. The GPC traces showed that the concentration of 40 kDa polymer **1** decreased with sonication time, while a new 20 kDa molecular weight species increased. Within the limits of detection, mass balance existed between the 40 and 20 kDa peaks throughout the experiment, and the sharpness of the new 20 kDa peak suggested that it had a relatively low polydispersity index (Figure 1a).[10] This result indicates that the 40 kDa polymer **1** cleaves at its midpoint into two 20 kDa fragments upon exposure to ultrasound. Similarly, the 60 kDa polymer **1** was also cleaved site-specifically into two 30 kDa fragments (Figure 1b).

The control 40 kDa sebacic acid link-functionalized polymer (**2**) was subjected to the same ultrasonic conditions. The 40 kDa peak corresponding to control polymer **2** slowly diminished with sonication time, and a broad peak emerged on its low mass side with an average molecular weight of ca. 20 kDa (Figure 1c). The full width at half-maximum (fwhm) value of the broad peak was 1.22 min, almost 3 times the fwhm value of the 20 kDa peak from sonication of 40 kDa polymer **1** (0.46 min), indicating that chain scission occurs near the center of control polymer **2**, although not at a specific bond.



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These initial experiments are consistent with the idea that the ultrasound-induced cleavage of polymer **1** occurs predominantly at a specific location within the poly(ethylene glycol) backbone. To directly confirm this concept, polymer **1** was prepared with a ^{13}C isotopic label on its cyano carbon. This polymer was subjected to ultrasonic conditions, and the products of the reaction mixture were analyzed by ^{13}C NMR spectroscopy. The spectra show the appearance of only one major new peak, tentatively assigned to cyanohydrin **3** as shown in Scheme 1.[11] By comparing the extent of degradation determined by ^{13}C NMR and the extent of degradation determined by GPC, a rough estimate of the extent of site specificity can be obtained. Under the conditions employed, greater than 70% of the fragmentation events occur at the azo group.[12] Interestingly, the major product that results from ultrasound-induced fragmen-

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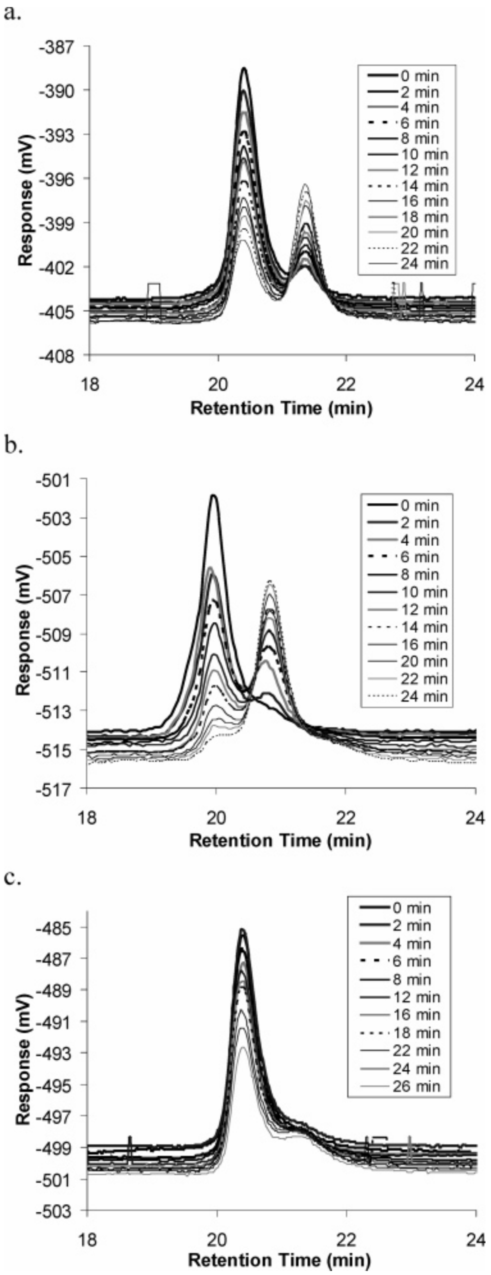


Figure 1. GPC traces depicting the effect of ultrasound on polymer **1** (40 and 60 kDa) and **2** (40 kDa). A 0.75 mg/mL solution of either polymer **1** or control **2** in acetonitrile was subjected to ultrasound, at 20 kHz, 8.7 W/cm^2, and 6−9 °C under argon. (a) Absolute peak areas of 40 kDa polymer **1** starting material and the 20 kDa cleaved fragments at timed intervals throughout sonication. The small 20 kDa peak at $t = 0$ is due to uncoupled 20 kDa mPEG-NH$_2$ starting material, from the synthesis of **1**, that could not be separated. (b) Absolute peak areas of 60 kDa polymer **1** starting material and the 30 kDa cleaved fragments at timed intervals throughout sonication. (c) Absolute peak areas of 40 kDa control **2** starting material at timed intervals throughout sonication.

tation (**3**) is different from the major products that result from thermolysis (**4** and **5**). Radical recombination is the major pathway that is followed when polymer **1** is subjected to thermolysis (Scheme 1). The absence of radical recombination[13] under ultrasound is consistent with a rapid separation of the radical pair, owing to the high shear conditions.

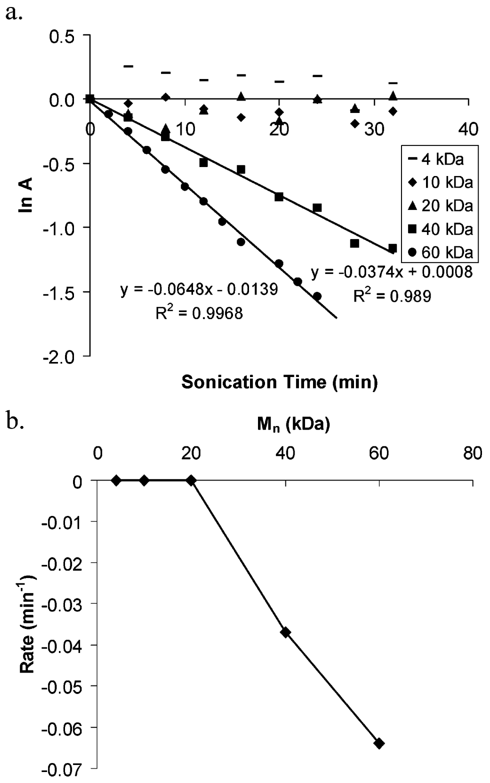


Figure 2. (a) Effect of chain length on the fragmentation rate of polymer **1** was determined by a first-order rate analysis of 4, 10, 20, 40, and 60 kDa **1** (0.75 mg/mL in acetonitrile) subjected to ultrasound at 20 kHz, 8.7 W/cm^2, and 6−9 °C under argon. The fragmentation rate was found to decrease with polymer molecular weight to a limiting value between 20 and 40 kDa. (b) Dependence of cleavage rate on polymer molecular weight.

Effect of Chain Length on Rate of Polymer Cleavage. Previous studies on the ultrasonic degradation of polymers in solution have demonstrated a chain length dependence on the rate of degradation.[1] Because the azo-centered polymer irreversibly breaks at its midpoint, its cleavage can be represented as

$$\mathrm{P}(x) \xrightarrow{k} 2\mathrm{P}(x/2) + \mathrm{N}_2 \tag{1}$$

where P(x) is polymer **1** and P(x/2) is the fragmentation product. Thus, the reaction should follow first-order kinetics with the degradation rate given by

$$-\mathrm{d}[\mathrm{P}(x)]/\mathrm{d}t = k[\mathrm{P}(x)] \tag{2}$$

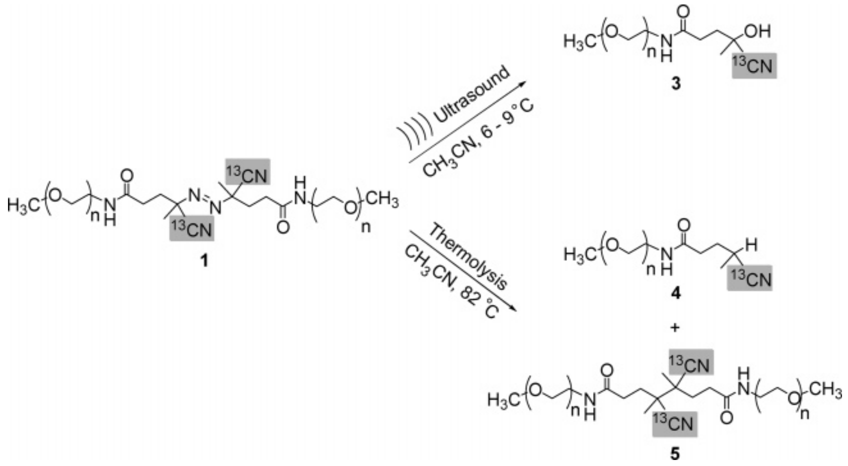
To determine the cleavage rate, the concentration of polymer **1** was first normalized at each timed interval according to the following equation

$$A = C_X/C_\mathrm{i} \tag{3}$$

where C_X is the concentration of polymer **1** at time X, C_i is the initial concentration of polymer **1**, and A is the normalized concentration. The final concentration was assumed to be zero, as expected if eq 1 is the only reaction taking place.[1,2] The natural logarithm of A was plotted against sonication time, and the rate of ultrasonic fragmentation was determined from the slope of the line (Figure 2a).

Polymers **1** of molecular weights 40 and 60 kDa were found to fragment on average at rates of 0.037 and 0.065 min^{-1}, with half-lives of 19 and 11 min, respectively, when subjected to pulsed ultrasound (0.5 s on, 1.0 s off) at 20 kHz, 8.7 W/cm^2, and 6−9 °C in acetonitrile under argon. These conditions were not sufficient to induce

Scheme 1



scission of the 4, 10, or 20 kDa **1**. These results indicate that the limiting molecular weight for the ultrasonic degradation of **1** is between 20 and 40 kDa and that longer polymer chains undergo a faster scission rate (Figure 2b). These data are consistent with previous studies and are a consequence of larger solvodynamic forces with larger molecules.[1−3]

Off-Center Cleavage. In the above examples, the weak bond used for site-specific cleavage was positioned in the center of the polymer backbone. Off-center polymers **1** and **2** were prepared in which the azo or sebacic acid link was flanked by a 10 and 30 kDa poly(ethylene glycol) chain. The sensitivity of the cleavage rate to the location of the link was studied by subjecting off-center 40 kDa **1** and off-center 40 kDa control **2** to ultrasound.

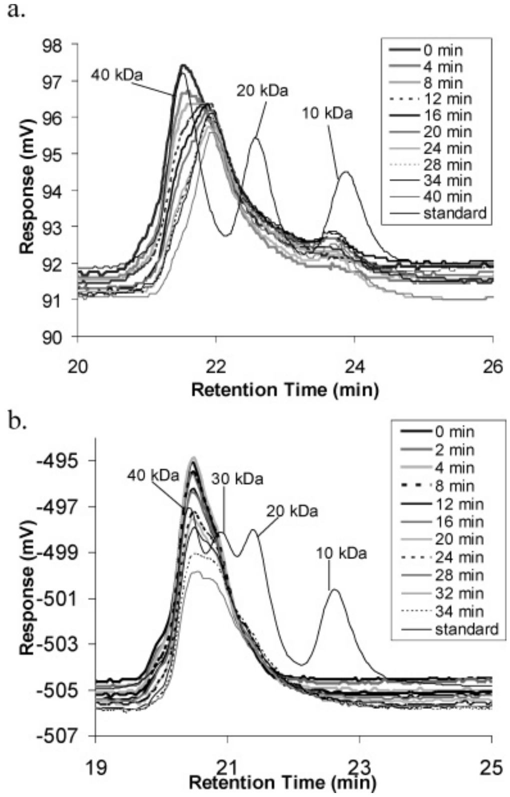


Figure 3. GPC traces depicting the effect of ultrasound on an off-center azo-functionalized polymer. (a) 40 kDa polymer **1** in which 10 and 30 kDa poly(ethylene glycol) segments flank the azo linkage was subjected to ultrasound at 20 kHz, 8.7 W/cm^2, and 6−9 °C under argon. The off-center polymer yielded 10 and 30 kDa fragments. (b) Absolute peak areas of the off-center 40 kDa **2** starting material at timed intervals throughout sonication. Cleavage products at 10 kDa were absent.

The GPC trace of off-center 40 kDa **1** showed a decrease in the initial 40 kDa peak area and an increase in the peak areas corresponding to 30 and 10 kDa species upon exposure to ultrasound (Figure 3a). Significantly, sonication of off-center control **2** produced no 10 kDa polymer (Figure 3b). Resolution limits and the presence of a 30 kDa impurity do not allow for quantitative determination of relative rates at this time. Nonetheless, our findings indicate that scission of the off-center azo linkage occurs competitively with near-center scission of the poly(ethylene glycol) repeat units. Thus, the single azo moiety is weak enough to break at a rate comparable to the collection of all other bonds, even those closer to the center of the polymer where solvodynamic forces are greatest.

In summary, ultrasound-induced site-specific cleavage of a polymer was accomplished by incorporating a single weak, azo linkage into the backbone of poly(ethylene glycol). The ultrasonic fragmentation of azo-functionalized polymers differs from the previously reported degradation of homopolymers or block copolymers in two important ways. First, the rate of ultrasonic cleavage is appreciably faster in the azo-centered polymers **1** due to the weak bond in the polymer backbone. In addition, the azo-functionalized polymer cleaves with a high degree of bond specificity, resulting in one type of chain end and fragments of low polydispersity. Ultrasound-induced site-specific cleavage of polymers could be extended as an alternative to thermal or photoinduced reactions. Further studies along these lines will be reported in due course.

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Supporting Information Available: Synthetic schemes, GPC traces showing the ultrasonic degradation of 4, 10, and 20 kDa azo-centered polymers **1**, and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The full-width at half-maximum value of the 20 kDa peak from sonication of 40 kDa **1** was 0.46 min.

(11) This assignment was made based on comparisons to small molecule models and the observation that the intensity of this peak increased during thermal degradation when oxygen was introduced into the system through an open condenser. See the Supporting Information for further details on the small molecule models.

(12) This estimate assumes the relaxation times of the nitrile carbons in starting material **1** and the fragmented polymer are the same. Because the fragmented polymer is expected to have longer relaxation times than starting material **1**, this assumption will cause an underestimate of the extent of site specific cleavage.

(13) To observe the radical coupling product, **5** would need to be stable to the ultrasound conditions. The rate of ultrasound-induced cleavage of coupling product **5** was found to be less than half of the rate of scission of polymer **1.** As stated in the text, radical coupling product **5** was not observed in the ^{13}C NMR of sonicated polymer **1**; therefore, we conclude that **5** does not form by ultrasound.

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