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Polyether Urethane Hydrolytic Stability after Exposure to Deoxygenated Water

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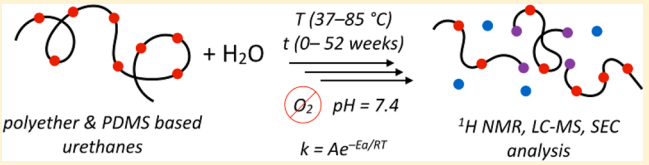
Supporting Information

ABSTRACT: A medical grade, commercially available polyether urethane, denoted PEU 80A, was exposed to both real time (37 °C) and temperature accelerated (55, 70, and 85 °C) hydrolysis conditions for a period of one year *in vitro*. Neutral pH and deoxygenated phosphate buffered saline exposure conditions mitigated the well-studied oxidation reaction, allowing for evaluation of hydrolysis events. The hydrolytic sensitivity of the PEU 80A was analyzed using nuclear magnetic resonance (NMR) spectroscopy, liquid chromatography−mass spectrometry (LC-MS), and size exclusion chromatography (SEC). We showed that the only obvious backbone chain scission event occurred at the urethane (carbamate) linkages. Using the widely applied Arrhenius model for accelerated predictions involving chemical reactions, we predict that a 50% reduction in PEU 80A molar mass would require approximately 80 years of exposure at 37 °C in the presence of excess water. The activation energy for urethane linkage hydrolysis of ∼90 kJ mol^{-1} extracted from this analysis is in agreement with previous reports, where the change in molar mass was accounted for by chain scission events at the urethane linkage. A similar analysis of polydimethylsiloxane (PDMS) modified urethanes PurSil 35 (P35) and ElastEon 2A (E2A), exposed to identical hydrolysis conditions, gave an equivalent activation energy for urethane hydrolysis, indicating that hydrolytic cleavage of backbone urethane linkages is not significantly impacted by the incorporation of PDMS into the urethane structure. However, as previously reported, the activation energy governing the observed molar mass reduction in these PDMS-urethanes is one-third that measured for the hydrolytic chain scission events at the urethane bond. These combined results suggest that the reaction(s) responsible for the observed molar mass changes in the PDMS-urethanes is not due to hydrolytic cleavage at the urethane linkages.



INTRODUCTION

As the cost of medical interventions rise, the demand for implantable medical devices with extended lifetime increases. As a result, significantly enhanced biostability of the polymeric materials used in the construction of these devices has become an important goal. Any *in vivo* degradation reactions of the polymers used in implantable devices must be slow enough such that any associated changes in the material properties do not render it ineffective during its expected lifetime. In the case of most polymer-based technologies, the primary reactions of concern *in vivo* are backbone hydrolysis and oxidation. Polyether urethanes (PEUs) have a long history of successful use as a cardiac lead insulation,[1] and both classes of degradation reactions have been widely studied. Numerous *in vivo* and accelerated *in vitro* studies have demonstrated that backbone oxidation and subsequent cleavage or cross-linking constitute the dominant biodegradation mechanism for PEU.[2] The oxidation reaction is not uniform throughout the material; rather, it occurs at the surface and is dependent on the local macrophage environment.[3]

In contrast to oxidation, the hydrolysis reaction occurs within the bulk of PEU due to hygroscopic nature of the material and the relatively fast rate of water diffusion as compared to hydrolysis kinetics.[4] Hydrolysis has been shown to occur at the urethane (carbamate) linkage, and activation energies (E_a) for this reaction have been reported to be ∼100 kJ/mol.[5−7] Furthermore, 4,4′-methylenedianiline (MDA), a hydrolysis byproduct, has been extracted under hydrolytic conditions such as steam sterilization from PEUs prepared using 4,4′-methylenediphenyl diisocyanate (MDI).[8] The chemical scheme for this PEU hydrolysis reaction is shown in Figure 1. Once cleaved from the solid polymer structure, MDA is expected to diffuse into the water phase as a result of its high water solubility.[9]

The understanding of PEU *in vivo* degradation mechanisms was largely developed by observation. In the beginning, device lifetimes were short, making real time preclinical testing feasible. As device lifetimes expanded, confidence in a PEU's biostability resulted from extrapolation of animal model results. As human *in vivo* experience with PEU was extended, observed biodegradation pathways were discovered and their associated rates studied. Now, current implant lifetime targets are a factor

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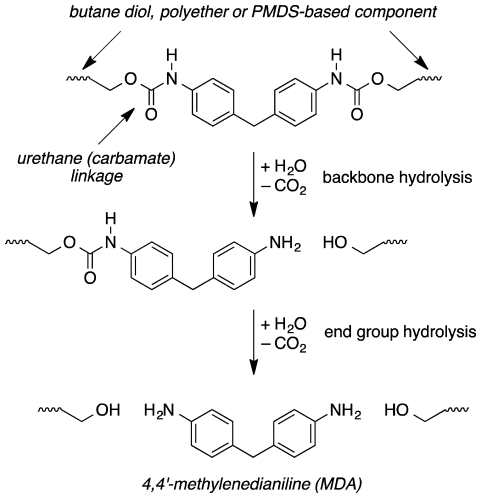

Figure 1. Hydrolysis of PEU occurs at the urethane linkage. A second hydrolysis reaction at the adjacent urethane linkage can liberate water-soluble MDA.

of 3−5 times the typical preclinical implant times. The design of new devices with established materials increasingly has relied on historical long-term human *in vivo* implant performance. However, such a strategy cannot be used for introduction of new polymer materials, where long-term human data are unavailable and the rates of *in vivo* degradation reactions are unknown. As a consequence, it is increasingly important for the medical device industry to utilize accelerated testing protocols, a common practice in other industries, to screen new materials for use in long-term implants.

We recently reported on the hydrolytic stability of new commercially available polydimethylsiloxane (PDMS) modified urethane materials.[11] In that work, we exposed two PDMS-urethane materials to deoxygenated water at 37 °C for a period of one year. Hydrolytic stability of the polymers beyond a year was estimated using the Arrhenius model,[10] where the rate of the chemical reaction at 37 °C was accelerated by increasing the temperature. We showed that acceleration temperatures up to 85 °C did not significantly affect the structure or morphology of the material. In addition, the overall solubility of water, a factor in applying the Arrhenius model, did not vary significantly over the temperature range employed. Accelerated testing predicted that material properties (tensile, abrasion, and fatigue) would be significantly compromised after 3−6 years of water exposure at 37 °C.[11,12]

To explore the differences in the hydrolysis rate between PEUs and more hydrophobic polydimethylsiloxane (PDMS)-urethanes, we have studied a particular PEU (PEU 80A, Shore 80A hardness) under the same hydrolysis protocol we recently used for the closely related PDMS-urethane materials.[11] The hydrolysis of the urethane (carbamate) bond in these materials was monitored using ^{1}H NMR spectroscopy and LC-MS analysis as a function of exposure time to deoxygenated phosphate buffered saline (PBS) solution. In this work, we show that the hydrolysis of PEU occurred at a reduced rate compared to PDMS-urethanes. We also present results that suggest the principal hydrolytic cleavage of PDMS-urethanes proceeds by a mechanism distinct from that in the PEUs.

EXPERIMENTAL SECTION

The protocols described below are directly related or identical to our previously reported procedure and are reproduced here for completeness.[11]

Materials. Elasthane 80A (denoted PEU 80A) (DSM Biomedical), Elast-Eon E2A (denoted E2A) (Aortech, International), and PurSil 35 (denoted P35) (DSM Biomedical) were received from the respective manufacturers. PEU 80A has a Shore hardness of 80A. E2A and P35 are also soft durometer materials with Shore hardness values of 90A and 80A, respectively. As-received pellets were dried and compression molded into 0.7 mm thick sheets at 220 °C. Rectangular test specimens (2.5 cm × 4 cm) were cut from the compression molded sheets.

Aging in PBS. The compression-molded polymer plaques (n = 7 for each sampling time point and exposure temperature for a total of n = 196; n = 15 additional tensile samples and n = 15 fracture mechanical samples were also included for each time point and temperature, but these samples were not part of the work herein) were aged in deoxygenated phosphate buffered saline (PBS) solution as described in our previous publication.[11] The (PBS) solution was obtained from Sigma-Aldrich (P5368). House nitrogen was continuously bubbled through the solutions to minimize the presence of oxygen. Periodic monitoring with an electronic oxygen probe (VWR symphony SP90M5) showed less than 4% of the saturation concentration of oxygen in the PBS at ambient conditions. The pH was periodically monitored and remained at pH = 7.4 ± 0.5 over the course of the aging experiments. Samples were aged under these conditions at four different temperatures (37, 55, 70, and 85 °C) for 1 year (52 weeks).

To avoid the complexities associated with the evaporative loss and subsequent replenishment of the test solution in the open system as well as changes in the volume of polymer contained in the solution (a result of periodic sample removal as time progressed), a second set of PEU 80A samples were aged in a closed system, where the ratio of polymer to water was held constant. 3 g of compression molded polymer sheets was placed in 15 mL of deoxygenated PBS solution. The solution was deoxygenated by bubbling with nitrogen until the oxygen probe showed less than 4% of the saturation concentration of oxygen in the PBS at ambient conditions. The vials were sealed and introduced to ovens that were blanketed with a continuous flow of nitrogen. These PEU 80A samples were aged at 70 and 85 °C for 16 weeks. We periodically sampled the water phase, replenished with PBS, deoxygenated, and returned the samples to the nitrogen-blanketed oven.

Nuclear Magnetic Resonance (NMR) Spectroscopy. The PEU 80A nonaged control and aged samples were dried and dissolved in THF-d_8 at a concentration of ∼20 mg mL^{-1}. Proton NMR spectra were acquired on a JEOL Eclipse 400 MHz NMR at room temperature. Spectra were processed with JEOL NMR software Delta 5.0 and peaks in the ^{1}H NMR spectra were integrated by setting the resonance at 7.35 ppm (protons ortho to the carbamate linkage on the phenyl rings) to 4. The peak assignment for the MDA produced post hydrolysis was confirmed by analyzing a 4,4′-methylenedianiline (MDA) standard in THF-d_8. ^{13}C NMR spectroscopy was also used to analyze the urethane hydrolysis reaction and confirm the peak assignments in the proton spectra. The fraction (percentage) of urethane hydrolysis was calculated by dividing the peak at 6.45 ppm (protons ortho to the amine on the phenyl rings) over the sum of peaks at 7.35 and 6.45 ppm (all the aromatic protons). This analysis was performed on five polymer samples for each exposure temperature and time point.

Liquid Chromatography−Mass Spectrometry (LC-MS). MDA in the solution phase of the closed experiment was quantified with LC-MS. The LC-MS consisted of a Waters Acquity LC separation module and an Applied Biosystem 4000 QTrap system. Separation was performed using an Acquity UPLC BEH C18 (1.7 μm, 2.1 × 50 mm) column at 45 °C. Solvent A was water (0.1% formic acid) and solvent B was acetonitrile (0.1% formic acid). Gradient elution was used with a flow rate of 0.4 mL min^{-1}. Solvent B was set to 0% for the first minute,

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increased to 90% between 2 and 3 min, and held constant at 90% for 0.6 min before decreasing to 0% at 3.8 min. Electrospray ionization was utilized for the mass spectrometry analysis. A 4 uL aliquot of the solution was injected into the system for each sampling point, and the data were analyzed with the Analyst 1.6 software package. The dominant mass peaks for MDA were Q1 at 199.1 m/z and Q3 at 106.2 m/z. Q1 is MDA with an added proton, $[M + H]^+$, while Q3 is from the fragmentation of MDA, where one side of the aniline is extracted, $[M\text{-}PhNH_2]^+$. The molecular drawings of these fragmented species are shown in the Supporting Information, Figure S2. MDA standards were used to build the calibration curve for quantification of MDA concentration. This analysis was performed in duplicate, and a new calibration curve was created at each sampling time point.

Molar Mass Determination. The relative molar masses of both the nonaged (control) and the solution aged specimens were evaluated using either an Agilent HP1100 or 1200 HPLC system fitted with two PLgel 10 μm MIXED-B columns and a UV detector (270 nm wavelength), operated with dimethylformamide (containing 0.05 M LiBr) as the mobile phase at a flow rate of 1 mL min^{-1} at 53 °C. The instruments were calibrated with 11 low dispersity polystyrene (PS) standards ranging from 600 to 600 000 g mol^{-1} obtained from Polymer Laboratories. For all size exclusion chromatography (SEC) experiments, a minimum of two samples (two injections each) were evaluated. Over the 52-week study, each data set included SEC measurements taken at a minimum of seven time points, at each of the four aging temperatures. As an internal reference, the time zero (nonaged control) data were reacquired at each time point.

RESULTS AND ANALYSIS

Urethane Bond Hydrolysis. Hydrolysis of a backbone urethane bond in these polyether urethanes results in cleavage of the backbone generating two chains. One contains an aromatic amine (postextrusion of CO_2 from the initially formed carbamic acid group) at the cleavage site and the other contains a hydroxyl group (see Figure 1). The presence of the terminal aromatic amine results in protons that resonate at 6.80 and 6.45 ppm in the NMR spectra and are distinct from the corresponding backbone aromatic resonances at 7.35 and 7.02. Assignment of the 6.80 and 6.45 ppm resonances was corroborated by comparison to MDA (see Supporting Information). The ^{1}H NMR signature of this terminal aromatic amine was used to quantify the number of urethane bond hydrolysis events as a function of water exposure time for PEU 80A. Figure 2 compares a non-water-exposed sample to a sample that was aged at the most accelerated conditions and longest water exposure time (85 °C for 1 year). The number of hydrolyzed urethane linkages was quantified by taking the integrated area of the peak at 6.45 ppm and normalizing it to the total number of urethane linkages (peak area of 7.35 ppm and peak area of 6.45 ppm; see the Experimental Section). Careful examination of the entire spectra showed no other obvious reactions. A small shift in the location of the aromatic proton resonances was apparent in the ^{1}H NMR spectra of free MDA when compared to the polymer (Supporting Information, Figure S1). This is expected since the different peak positions are consistent with isolated hydrolysis events that leave the aromatic amine moiety still connected to a chain end. Further hydrolysis of this end aromatic unit would liberate free MDA and leave another hydroxyl end group (Figure 1).

Because MDA is water-soluble, free MDA resulting from the hydrolysis of two adjacent urethane bonds can diffuse from the solid polymer and into the water phase. When this happens, NMR evidence of the chain scission event is lost from the solid polymer specimen. To account for MDA loss from the solid polymer into the water phase, the water phase in the closed

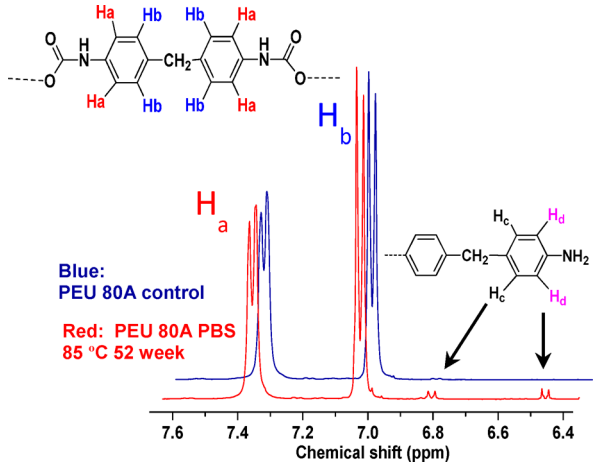

Figure 2. ^{1}H NMR spectroscopy was used to quantify the hydrolyzed urethane bonds in the PEU 80A solid polymer. The aromatic amine-containing chain end group and the free MDA formed after the hydrolytic chain scission reaction can be identified by the associated aromatic proton resonances at 6.80 and 6.45 ppm. These peaks were assigned by comparison to monomeric MDA (see Supporting Information).

system experiment was monitored by LC-MS for the presence of free MDA for a period of 16 weeks. At 37 and 55 °C, the extent of the hydrolysis reaction based on analysis of the ^{1}H NMR data was <0.3% at 1 year. Because of this low extent of reaction, we focused our search for free MDA on the higher temperature experiments (70 and 85 °C) with correspondingly higher extents of hydrolysis. Figure 3 shows the LC-MS chromatograms used to quantify the MDA in the aqueous phase for exposure temperatures of 70 and 85 °C. As the water exposure time increased, the concentration of MDA in the aqueous phase increased. Moreover, the concentration at a particular sampling time increased with temperature. Using a calibration curve (see Supporting Information, Figure S3), we

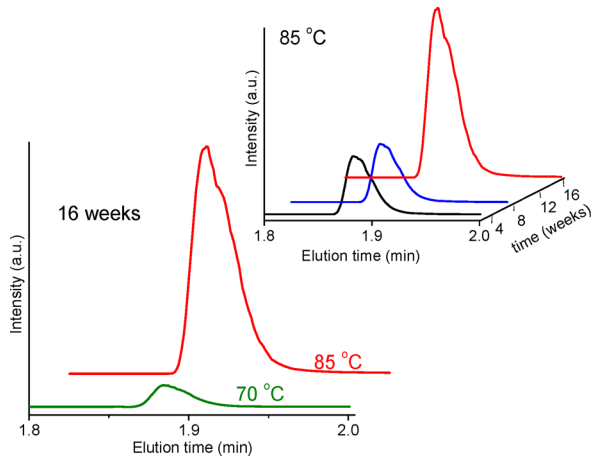

Figure 3. LC-MS was used to quantify the free MDA in the aqueous phase when PEU 80A was aged in a closed system. A plot of intensity vs elution time is shown for the 16-week time point at exposure temperatures of 70 and 85 °C. In the inset, the complete set of 85 °C data is shown as a function of exposure time: 4, 8, and 16 weeks. The detector intensity was calibrated to determine the MDA concentration (see Figure S3 for calibration curve). The concentration of MDA in the aqueous phase increased with both hydrolysis time and temperature. For the complete set of 70 °C data, see Figure S4.

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quantified the concentration of MDA in the PBS solution as a function of water exposure time at 70 and 85 °C. The concentration of MDA in solution was normalized to the total number of methylene diphenyl diisocyanate (MDI) chemical moieties in the nonaged polymer control sample (PEU 80A composed of 35 wt % MDI as determined by ^{1}H NMR spectroscopy).

The extent of urethane hydrolysis was calculated by summing the concentration of terminal aromatic amines moieties (quantified in the solid polymer by ^{1}H NMR spectroscopy as described above; data shown in Supporting Information, Figure S6) and the concentration of MDA in the aqueous phase (as quantified by LC-MS; data shown in Supporting Information, Figure S5). Two hydrolysis events necessarily occurred for every MDA molecule observed stemming from backbone hydrolysis, and this factor of 2 was taken into account in evaluating the total level of hydrolysis. Figure 4 is a plot of the

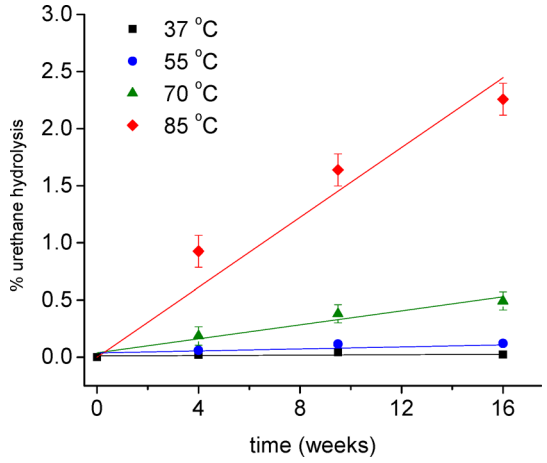

Figure 4. Total PEU 80A urethane hydrolysis percentage was determined by adding the number of aromatic amino group chain ends in the solid polymer (measured using ^{1}H NMR spectroscopy) and 2 times the free MDA (measured using LC-MS) that accumulated in the aqueous phase during the hydrolysis experiment at 70 and 85 °C. The data at 37 and 55 °C are derived from the ^{1}H NMR data only. At these low extents of hydrolysis, loss of MDA to the water phase was not detected in the open system.

number of urethane hydrolysis events as a function of water exposure time and temperature as a percentage of the total number of urethane linkages in the PEU 80A. The linearity of the data over time suggests a constant overall reaction rate for hydrolysis of the urethane linkage (either backbone cleavage or end cleavage). The linearity of the 37 and 55 °C data in the absence of accounting for MDA loss to the water phase suggests that water phase concentrations of MDA are low when the overall extent of reaction is low, as expected.

Molar Mass Change. Each hydrolysis event at a urethane linkage in the polymer backbone (i.e., not at a chain end) results in a halving of the number-average molar mass of that particular chain. Thus, the total fraction of chain scission events is inversely proportional to the number-average molar mass of the resultant polymer sample; the more chain scission, the lower the molar mass. The inverse of the PEU 80A number-average molar mass as determined by SEC (relative to polystyrene standards), normalized to the initial molar mass prior to hydrolysis, is plotted as a function of time for each experimental hydrolysis temperature in Figure 5. The initial

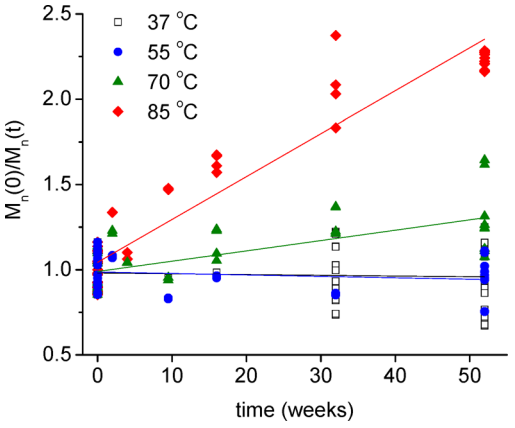

Figure 5. Relative molar mass of the PEU80A samples after exposure to PBS buffer as a function of time at the temperatures indicated. The relative molar mass did not change significantly for 37 or 55 °C exposure temperatures over 52 weeks. However, the molar mass decreased for the higher exposure temperature of 70 and 85 °C.

PEU80A molar mass was 160 ± 20 kg mol^{-1} by SEC relative to polystyrene standards. The molar mass for water exposure temperatures of 37 and 55 °C showed no statistically significant change over a period of 1 year. However, reductions in the polymer molar mass were apparent for aging temperatures of 70 and 85 °C. The linearity of the data shown in Figure 5 is consistent with a constant reaction rate. The hydrolysis reaction rate is expected to be linear in time since the concentration of urethane linkages, and the concentration of soluble water is essentially constant over the course of the reaction. (There are 280 urethane linkages per each 100 000 g/mol chain, where on average <2 backbone cleavage reactions are occurring per chain at the longest times and most accelerated conditions (85 °C, 1 year), resulting in a molar mass reduction to approximately one-third of the starting molar mass.) For the largest molar mass observed, approximately two urethane bonds reacted per chain, resulting in a <1% reduction in the urethane linkage concentration. Furthermore, any reacted water is readily replenished by diffusion from the buffer solution. The equilibrium water solubility was shown previously to be at 2 wt % over the course of the 1 year exposure time.[11] Furthermore, PEU 80A samples achieved this equilibrium weight gain in less than 30 min when soaked in water. Assuming a hydrolysis stoichiometry of one to one, where one water molecule reacts with one urethane linkage, the rate of water replenishment via diffusion is 6 orders of magnitude greater than the rate of reaction at the most accelerated reaction conditions (see Supporting Information). As soon as a water molecule is consumed by the hydrolysis reaction, it is replaced by diffusion of a water molecule from the solution. Because of the constant water concentration and the very small reduction in the urethane linkages, this reaction is pseudo-zero-order; therefore, the linear relationship in both Figure 4 and Figure 5 is expected. The scatter in the molar mass data is attributed in part to allophanate formation, a reaction that is known to occur in polyether urethanes like PEU 80A when the NCO/OH ratio is greater than one during the synthesis.[13]

Temperature Dependence of the Hydrolysis Reaction. As discussed in detail in our previous work,[11] the slope of the least-squared fit to the molar mass data in Figure 5 is proportional to the rate constant for backbone hydrolysis (k') at a given temperature. Likewise, the slope of the least-squared

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fit to the data in Figure 4 is proportional to the rate constant for urethane hydrolysis (k'') as measured by ^{1}H NMR spectroscopy and LC-MS as described above. In the case of the chemical analysis, all urethane hydrolysis events were counted, both backbone and chain end cleavage of MDA. We make the assumption that the rate of backbone urethane hydrolysis and urethane hydrolysis that liberates MDA from a chain end as equivalent reactions from a kinetics standpoint to simplify the analysis. The temperature dependence of both the urethane bond hydrolysis rate constant (Figure 4) and the corresponding rate constant for the molar mass decrease (Figure 5) can be evaluated using an Arrhenius analysis where E_a is the apparent activation energy, R is the gas constant, T is the absolute temperature, A is the Arrhenius prefactor, and k' (or k'') is the slope of the data in Figure 5 (or Figure 4) at each temperature.

$$k' \text{ (or } k'') = Ae^{-E_a/RT}[\text{bond}]_0[H_2O]_0 \quad (1)$$

In the case of the overall change of molar mass, any chain scission event is captured regardless of the specifics of the hydrolysis (or other) event. However, the SEC measurement will not be sensitive to hydrolysis of a urethane bond at the chain end that liberates MDA. In the ^{1}H NMR/LC-MS data set, the urethane linkage was specifically monitored, and any reaction that cleaves the urethane linkage is accounted for in the analysis. Therefore, for the ^{1}H NMR/LC-MS data set, eq 1 can be modified to assign the specific chemical linkage, $[\text{bond}]_0 = [U]_0$, where $[U]_0$ is the initial concentration of urethane (carbamate) linkages.

Because the polymer density and water content in the solid polymer are not strongly temperature dependent as was previously shown,[11] the apparent activation energy can be extracted by plotting the data according to eq 2

$$\ln(k'(\text{or } k'') + C) = -\frac{E_a}{RT} \quad (2)$$

Figure 6 shows the natural log of the slope defined by the least-squared fit to the molar mass data in Figure 5 ($k' + C$) as a function of absolute temperature at 70 and 85 °C. In addition, the natural log of the slope defined by the least-squared fit to the chemically analyzed data in Figure 4 ($k'' + C$) is plotted as a function of absolute temperature at 37, 55, 70, and 85 °C.

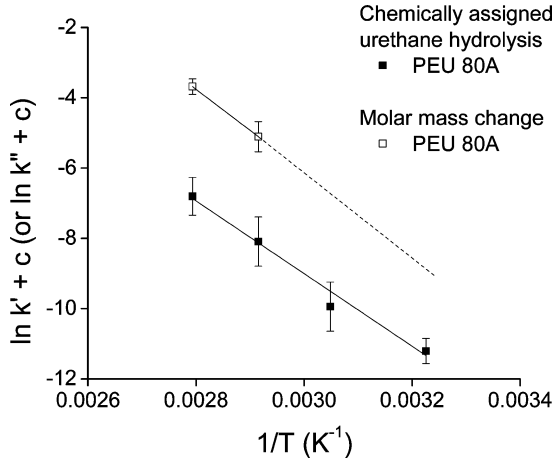

Figure 6. Arrhenius plot for reaction rates derived from the total urethane hydrolysis reaction and the overall change in molar mass (PEU80A). The slope of the data in these plots is equal to $-E_a/R$.

The linearity of the urethane hydrolysis data is consistent with an activated chemical process. The slope of the molar mass and the ^{1}H NMR/LC-MS data sets give activation energies (E_a) of 94 ± 18 and 90 ± 9 kJ mol^{-1}, respectively.

DISCUSSION

The results presented in the previous section demonstrate that exposure of PEU 80A to deoxygenated PBS for extended periods of time results in hydrolytic chain scission of urethane linkage. Because the urethane linkages are along the backbone of the polymer chain, the overall molar mass is necessarily reduced. The activation energy for hydrolytic cleavage of the urethane linkage was determined to be ≈90 kJ mol^{-1}, a result consistent with literature reported activation energies that range from 73 to 115 kJ mol^{-1}.[5−7] Based on the Arrhenius analysis (Figure 6), the high temperature data can be used to make predictions about the long-term stability at lower temperatures as follows: $t_{ref} = b_T t$, where $b_T = e^{(E_a/R)((1/T_{ref}) - (1/T))}$ is the time acceleration factor, t is the real time of the experiment, and t_{ref} is the time for the observed effect at the reference temperature, T_{ref}.[14] Using E_a = 90 kJ/mol, T_{ref} = 310 K (37 °C, body temperature), and T = 358 K (85 °C), b_T was calculated to be 108. Therefore, when the PEU 80A hydrolysis reaction is carried out at 85 °C, the rate of backbone hydrolysis is more than 2 orders of magnitude larger than at 310 K (37 °C). Applying this scaling factor, b_T =108, to the 85 °C molar mass data, for this *unique* situation where the oxygen was excluded from the experiment, thus significantly attenuating oxidative reactions, the molar mass of PEU 80A would drop by 50% after about 80 years of water exposure time. However, it is well established that PEUs are susceptible to oxidation, and it is oxidative degradation that limits the useful *in vivo* lifetime of PEU 80A.[3,15]

To compare the hydrolytic behavior of the PEU 80A to the PDMS-modified urethanes P35 and E2A we studied previously,[11] we generated a master curve that predicts the long-time degradation behavior of the PEU 80A using the calculated acceleration factors (see Figure S12). The accelerated time data were fit to a linear expression, and we included the resulting linear relationship on our previously reported master curve for the PDMS-modified urethanes (Figure 7). This comparison highlights the relative hydrolytic instability of the PDMS-modified urethanes as compared to PEU 80A over the same reduced time frame of approximately 7 years.

It is significant that the activation energy calculated from the molar mass data is, within experimental error, equivalent to the activation energy calculated from the data set that specifically followed the hydrolysis of the PEU 80A urethane linkage. This equivalency suggests that hydrolytic cleavage of the urethane bond accounts for the observed molar mass reduction in its entirety. However, not all hydrolytic cleavage reactions result in a measurable molar mass decrease. After the first hydrolysis event, hydrolysis of an adjacent urethane bond will result in formation of MDA. Because MDA has a molar mass of 198 g mol^{-1}, this adjacent hydrolysis event cannot be resolved in the molar mass data by SEC. The urethane hydrolysis reactions considered here must occur consecutively. That is, the molar mass reducing urethane reaction must occur first, followed by the cleavage reaction of the adjacent urethane bond. For the case of such consecutive reactions, the activation energy of the rate-limiting reaction is equivalent to the overall activation energy.[16]

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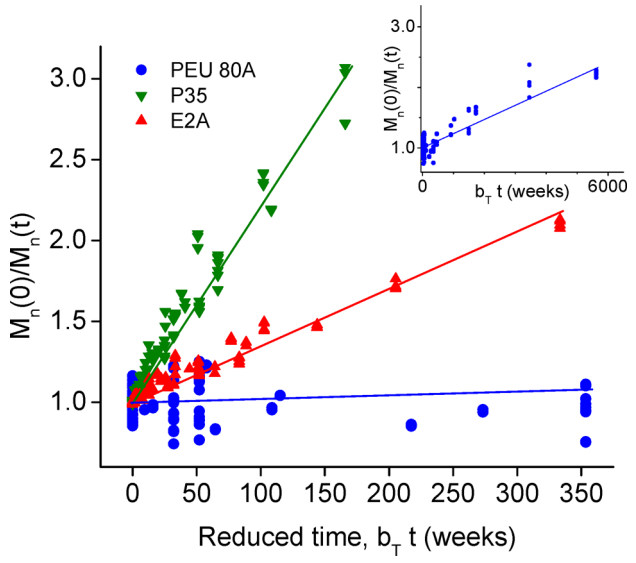

Figure 7. Comparison of the hydrolysis master curves for previously reported PDMS-modified urethanes P35 and EA2 (reproduced from ref 11) and PEU 80A using the calculated b_T acceleration factors for each of the samples and temperatures. The linear fits to all the data sets were forced through $M_n(0)/M_n(t) = 1$. All the data are shown for in the larger plot for the P35 and EA2 PDMS-modified urethanes. While the fit for the PEU 80A includes all the data (see the inset and Figure S12), only the data up to a reduced time of 375 weeks are shown in the larger plot for comparative purposes.

There is evidence that the molar mass reducing backbone urethane reaction is the rate-limiting reaction, thus the reason for equivalency of the chemical and molar mass derived activation energies. Steam sterilization of a polyetherurethane, having chain ends capped with MDI, resulted in an increase in free MDA without a significant decrease in molar mass.[17] Thus, the MDA cleavage reaction must have an activation energy that is lower than the backbone cleavage reaction. Therefore, in the case of the two consecutive urethane reactions considered here, our data are consistent with the backbone hydrolysis reaction being rate-limiting.

The identical ^{1}H NMR spectroscopic analysis was performed on the PDMS-modified urethanes P35 and E2A after samples were exposed to deoxygenated PBS 37, 55, 70, and 85 °C for a period of 52 weeks. Plots of percent urethane hydrolysis versus water exposure time are included in the Supporting Information (Figure S8 for P35 and Figure S9 for E2A). Table 1 compares the previously reported activation energies

Table 1. Activation Energies Derived from the Arrhenius Plot

polymer	urethane linkage E_a (kJ mol^{-1})	molar mass E_a (kJ mol^{-1})
PEU80A	90 ± 9	94 ± 18
E2A	70 ± 6	36 ± 6[a]
P35	83 ± 8	24 ± 6[a]

[a]Previously published data.[11]

calculated from the molar mass data to the activation energies calculated from the urethane linkage hydrolysis by ^{1}H NMR spectroscopic data.

When only the urethane bond was considered, by analysis of the ^{1}H NMR data, the activation energy for hydrolysis of the urethane linkage in the PDMS-modified urethanes was within one or two standard deviations to that measured for the urethane linkage hydrolysis in PEU 80A. This result suggests that the chemistry occurring at the urethane bond remains unchanged when PDMS replaces portions of the polyether urethane soft segments. However, in the case of the PDMS-urethanes, the overall molar mass reduction is much more rapid and proceeds with an activation energy that is approximately one-third that indicated for the urethane linkage hydrolysis. The difference between the relatively large urethane bond derived activation energy and the relatively low molar mass derived activation energy implies that reactions at the urethane bond do not account for the total molar mass loss observed in the PDMS-urethane polymers alone. Furthermore, the lower activation energy determined for the PDMS-urethanes based on molar mass reduction indicates that a second reaction site dominates the reaction kinetics, resulting in the observed changes in molar mass.

TRANSLATION TO PRACTICE

A distinct reaction with a significantly lower activation energy governs the erosion of polymer molar mass in the PDMS-urethane polymers having a mechanical property degradation at body temperature that is significantly faster than for traditional nonmodified polyether urethane materials. This is demonstrated by analysis of the previously reported nonaccelerated body temperature data in both the PDMS-modified urethanes and the PEU 80A urethane.[11] In PEU 80A, there was no statistical change in the molar mass after 1 year of water exposure at 37 °C. In contrast, the molar mass of E2A dropped by 6% and the molar mass of P35 dropped by 35% after 1 year of water exposure at 37 °C. The linearity of the temperature accelerated data indicated the observed rate of molar mass decrease would continue for at least as long as 6 years for E2A and 3 years for P35, where the molar masses achieved after these time frames would be low enough to result in a mechanical property (tensile, abrasion, fracture mechanics) decrease.[12] PEU 80A, in contrast, has a hydrolysis activation energy that is 3 times higher than that for the PDMS-modified materials. As a result, the urethane bond hydrolysis reaction at body temperature is not a dominant event in any of the materials considered, PEU 80A, E2A, or P35.

PEU 80A has been shown to be susceptible to oxidative attack at ether linkages. The activation energy for oxidation of the ether linkage has been reported to be 18−21 kJ mol^{-1}.[18] For the case of simultaneous reactions, the rate and nature of the dominate reaction will be a function of the available reactants, the temperature of reaction, and the activation energy. At the same temperature and reactant concentrations, oxidation of the ether bond, rather than hydrolysis of the urethane bond, likely dominates molar mass changes in PEU 80A. By substituting PDMS for a portion or all of the ether bonds, and thus reducing the fraction of ether bonds, the concentration of water in the polymer decreases due to the greater hydrophobicity of the polymer as compared to PEU 80A. As a result, the rate of the urethane hydrolysis and ether bond oxidation is proportionally reduced. These aspects suggest that the accelerated rate of molar mass decrease and stability of the PDMS modified polymers is the result of an unanticipated reaction.

We note that the PDMS in the structure of the PDMS-modified urethane materials can result in greater lipid solubility for these materials as compared to the PEU 80A polymers. Lipid adsorption can make polymers more hydrophobic, further

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reducing the availability of soluble water and thus decreasing the rate of hydrolysis *in vivo*. (Here we note that the nanoscale segregation of hydrophobic and hydrophilic polymer blocks in the material may result in the sequestration of lipid on a microscopic scale, which may or may not influence the effective concentration of water available for hydrolysis and chain cleavage.) For example, the weight fraction of cholesteryl esters in subcutaneous rabbit tissue is relatively high.[19] Absorption of lipid into the polymer could reduce the relative amount available water and retard the rate of hydrolysis *in vivo*. In contrast, human blood has much less lipid on a weight basis. Therefore, the *in vitro* PBS exposure conditions will likely result in water concentrations in the polyurethanes that are more similar to those that would be achieved in the bloodstream than a polymer in the subcutaneous tissue of a rabbit. This study, by design, was carried out targeting the highest practically achievable concentration of water in the polymers, and therefore hydrolysis rates observed are the result of a situation at or near the upper limit of water concentration in polyurethanes being studied.

SUMMARY

The reactions that dominate biomaterial degradation *in vivo* are hydrolysis and oxidation.[20] For PEU, numerous literature references implicate oxidation as the primary source of failure in implanted devices.[18,15] In this work we focused solely on characterizing the *in vitro* hydrolysis of PEU 80A when exposed to deoxygenated water at temperatures ranging from 37 to 85 °C. Polymer molar mass and chemical stability were monitored by SEC, ^{1}H NMR spectroscopy, and LC-MS. We demonstrated that backbone urethane bonds undergo chain scission through reaction with water governed by an activation energy of ∼90 kJ mol^{-1}; this finding is consistent with previously reported kinetics for urethane hydrolysis. These results anticipate that about 80 years are required to halve the PEU 80 molar mass by hydrolysis in the presence of excess water at 37 °C. Significantly, we obtained the same activation energy for hydrolysis of the urethane linkages in PDMS-modified urethane polymers. As shown previously using the same accelerated test, the molar mass of PDMS-modified urethane polymers decreases much more rapidly upon exposure to water than for PEU 80A. The activation energy for that molar mass decrease is approximately one-third of the ∼90 kJ/mol value reported here for PEU 80A. These combined results implicate chain scission through the cleavage of backbone bonds other than the urethane linkages in the PDMS-modified urethane polymers.

Note added in revision: During the review of this manuscript, a publication entitled "Limitations of predicting in vivo biostability of multiphase polyurethane elastomers using temperature-accelerated degradation testing" by Padsalgikar et al. appeared in *J. Biomed. Mater. Res., Part B*.[21]

ASSOCIATED CONTENT

Supporting Information

Experimental details; Figures S1−S12. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare the following competing financial interest(s): Marc A. Hillmyer and Frank S. Bates are paid consultants of Medtronic Incorporated.

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