Scalable Synthesis of Degradable Copolymers Containing *α*-Lipoic Acid via Miniemulsion Polymerization

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Abstract

A robust method is described to synthesize degradable copolymers under aqueous miniemulsion conditions using *α*-lipoic acid as a cheap and scalable building block. Simple formulations of *α*-lipoic acid (up to 10 mol%), *n*-butyl acrylate, surfactant, and costabilizer generate stable micelles in water with particle sizes <200 nm. The ready availability of these starting materials facilitated performing polymerization reactions at large scales (4 L), yielding 600 g of poly(*n*-butyl acrylate–*stat*–*α*-lipoic acid) latexes that degrade under reducing conditions (250 kg mol^{-1} → 8 kg mol^{-1}). Substitution of *α*-lipoic acid with ethyl lipoate further improves the solubility of dithiolane in *n*-butyl acrylate, resulting in copolymers that degrade to even lower molecular weights after polymerization and reduction. In summary, this simple and scalable strategy provides access to large quantities of degradable copolymers and particles using cheap and commercially available starting materials.

Introduction

Controlling polymer degradability has become increasingly important as the plastic waste crisis continues to garner public attention.[1–3] A variety of strategies have been developed to improve the degradability of common yet environmentally persistent plastics, including catalytic depolymerization,[4–7] backbone editing,[8,9] and specialty comonomers introduced during the polymerization itself.[10–12] Conceptually, a comonomer approach using existing infrastructure is especially appealing as a simple extension of syntheses already being performed on an industrial scale. Indeed, proof-of-principle experiments have demonstrated the viability of incorporating degradable comonomers into polymers derived from all of the major polymerization techniques spanning anionic,[13–15] cationic,[16–18] metathesis,[19–21] and radical[10,11,22] mechanisms. However, a key challenge shared by these examples is scalability. Although the societal and commercial motivation is clear, degradable comonomers are often difficult to synthesize, costly, and even unstable toward extended storage. It is therefore not surprising that such systems, while numerous, are typically relegated to demonstrations in research laboratories at small scales.

A particularly versatile technique for producing degradable polymers that could have far-reaching implications at scale involves comonomers which undergo radical ring-opening polymerization leading to the introduction of degradable backbone units. One benefit of this strategy lies in the potential breadth of polymers that can be impacted, including systems based on styrene derivatives,[23,24] methacrylates,[15] acrylates,[25,26] and acrylamides.[27,28] Historically, cyclic ketene acetals were a popular class of cyclic monomer that ring opens radically to form esters along the polymer backbone when copolymerized with various vinyl monomers.[24,29,30] Motivated by challenges in the reactivity and stability of cyclic ketene acetals, Gutenkunst,[31,32] Roth,[33,34] Guillaneuf,[10,25,35] and Johnson[36] recently demonstrated the remarkably efficient copolymerization

of dibenzo[c,e]oxepane-5-thione (DOT) with acrylates, methacrylates, and styrene, yielding thioesters in the backbone that can be degraded under basic conditions. Like cyclic ketene acetals, the synthesis of DOT and related derivatives requires multiple steps and harsh chemistry, limiting the scale at which copolymerizations can be performed conveniently.

An appealing alternative to specialty monomers such as cyclic ketene acetals and DOT is the health supplement known as α-lipoic acid.[37] Already available in kilogram quantities from Amazon and other consumer-facing retailers, α-lipoic acid is cheap, biocompatible, and biosourced. Notably, α-lipoic acid is also polymerizable—its unique five-membered dithiolane heterocycle contains a strained disulfide bond that ring opens under radical (as well as anionic[38,39] and cationic[40]) conditions. Following pioneering work by Tsarevsky,[41,42] Endo,[43,44] and Tian,[45,46] we have studied in detail the copolymerization behavior of α-lipoic acid with various acrylate and acrylamide derivatives.[26] The degradability of α-lipoic acid–containing copolymers is highly tunable, creating opportunities to design advanced materials such as sustainable pressure-sensitive adhesives.[22]

Although α-lipoic acid provides compelling degradability characteristics at low cost, adopting this monomer at industrial scales requires the development of polymerization reactions beyond a batch format. Indeed, many acrylate-based materials found in everyday life—from paints to adhesives, coatings, and foams—are synthesized via aqueous emulsion polymerization wherein monomers remain dispersed as droplets in water.[47,48] Such emulsions have myriad advantages over traditional batch reactions, including consistently low viscosity, better energy transfer, and increased molecular weight through compartmentalization effects.[49–51] There are many variants of this general idea that differ subtly by mechanistic details and physical properties such as particle size; examples include microemulsions, miniemulsions, traditional emulsions, and

suspensions.[47,48,52] Leveraging the scalability of α-lipoic acid and one of these emulsion polymerization techniques in tandem would represent a valuable step toward the design and synthesis of degradable polymers under industrially relevant conditions.

To address this challenge, here we demonstrate the aqueous miniemulsion copolymerization of α-lipoic acid with *n*-butyl acrylate (**Figure 1**). Highlighting the inherent scalability of this approach, more than 500 g of polymer was isolated from a 4-liter emulsion reaction using commercially available starting materials and equipment that is readily available in research laboratories worldwide. Incorporating a related comonomer—the ethyl ester of α-lipoic acid (ethyl lipoate)—circumvents solubility limitations imposed by α-lipoic acid alone and further increases the maximum loading of degradable units that can be readily incorporated into these polymers. In summary, the combination of miniemulsion polymerization and α-lipoic acid as a feedstock is a simple, cheap, accessible, and scalable strategy for accessing degradable copolymers based on C–C backbones.

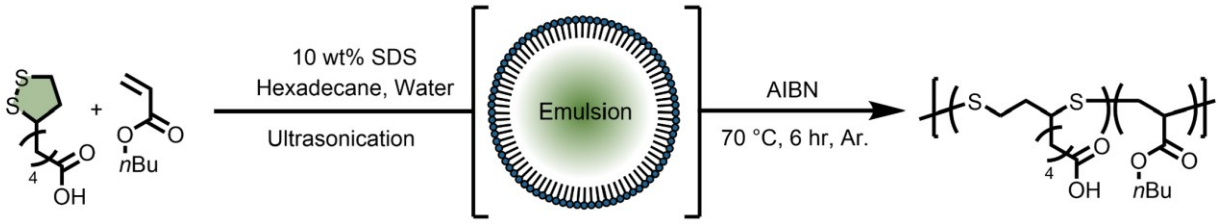

Figure 1. Miniemulsion polymerization of α-lipoic acid with *n*-butyl acrylate.

Results and Discussion

To develop a method for scalably producing degradable vinyl polymers with widely used industrial processes, miniemulsion polymerization was selected because it is simple to access

stable emulsions with good monomer tolerance and tunable reaction kinetics.[52] Emulating standard industrial conditions, sodium dodecyl sulfate (SDS) was chosen as the surfactant and hexadecane as a costabilizer.[25] For all reactions, the oil-soluble initiator azobisisobutyronitirile (AIBN) was added to confine initiation within micelles and mitigate the formation of coagulum. Because one key to a successful miniemulsion polymerization is the formation of stable monomer droplets evenly dispersed in the aqueous phase,[53] SDS concentration was initially optimized.

A key benefit of miniemulsions is their robust stability even well below the critical micelle concentration of a given surfactant (e.g., 8.2 mM for SDS).[54] Indeed, SDS concentrations as low as 1 wt% (0.42 mM) produced stable emulsions containing α-lipoic acid (Figure S1, S2) and *n*-butyl acrylate (*n*BA). Encouragingly, minimal changes were observed as the concentration of SDS increased further (Figure S3). Using 10 wt% (4.2 mM) SDS as a representative example, the effect of α-lipoic acid loading was evaluated from 1–10 mol%. An immediate reduction in particle size was observed in all cases as the reaction progressed, followed quickly by a plateau that was insensitive to α-lipoic acid content (**Figure 2a**). Following polymerization, the polymer particles remained stable with a narrow size distribution—another benefit of miniemulsion polymerization (**Figure 2b**). Encouragingly, polymer particles both during and after polymerization stayed below the radius for qualification as a miniemulsion (average radius $r < 250$ nm). After polymerization, the average particle radius was measured to be 33 ± 6 nm for polymers containing 5 mol% α-lipoic acid and 38 ± 8 nm for those containing 10 mol% α-lipoic acid. The polymer particle size was tunable with changes in surfactant concentration, however, even the largest micelles made with the smallest concentration of surfactant were below the threshold to be considered a miniemulsion (1 wt% SDS, $r = 110 \pm 20$ nm, Figures S1, S2). In contrast to particle size, the rate of conversion from monomer to polymer does depend more heavily on α-lipoic acid content as measured by ^{1}H

nuclear magnetic resonance (^{1}H NMR) spectroscopy (**Figures 3a**, S4–S7). At all α-lipoic acid loadings up to 10 mol%, high conversions were achieved (>95%), however, the rate of reaction decreased as α-lipoic acid content increased. Note that attempting to run polymerizations at even higher loadings of α-lipoic acid, e.g., 15 mol%, resulted in yellow coagulum which separated from the emulsion. While ^{1}H NMR spectroscopy demonstrated quantitative conversion of the monomer found in the oil phase at such high loadings, it was clear that a significant fraction of α-lipoic acid monomer units were not incorporated into polymer chains. This result is attributed to the solubility limit of α-lipoic acid in *n*-butyl acrylate (9.6 mol%, 0.756 mol/L, Figure S8), above which inefficient emulsification and polymerization is expected. Notably, under ideal conditions (<9.6 mol% α-lipoic acid), molecular weights achieved in miniemulsion (~200 kg mol^{-1}) were comparable to control samples synthesized in batch via analogous uncontrolled radical polymerization.[22] Furthermore, as expected, no gelation was observed in any sample, underscoring the lack of branching or crosslinking for polymer chains generated in each latex. To characterize the actual content of α-lipoic acid in a given polymer, its repeat units were methylated using trimethylsilyl diazomethane (TMS-diazomethane) to form the methyl ester, which has a unique and well-separated resonance in the ^{1}H NMR spectrum (Figure S9–10).[55] (Note: follow all safety protocols when handling TMS-diazomethane.) Targeted values based on feed ratios closely aligned with those measured experimentally for copolymers synthesized at high conversions (**Figure 3b**).

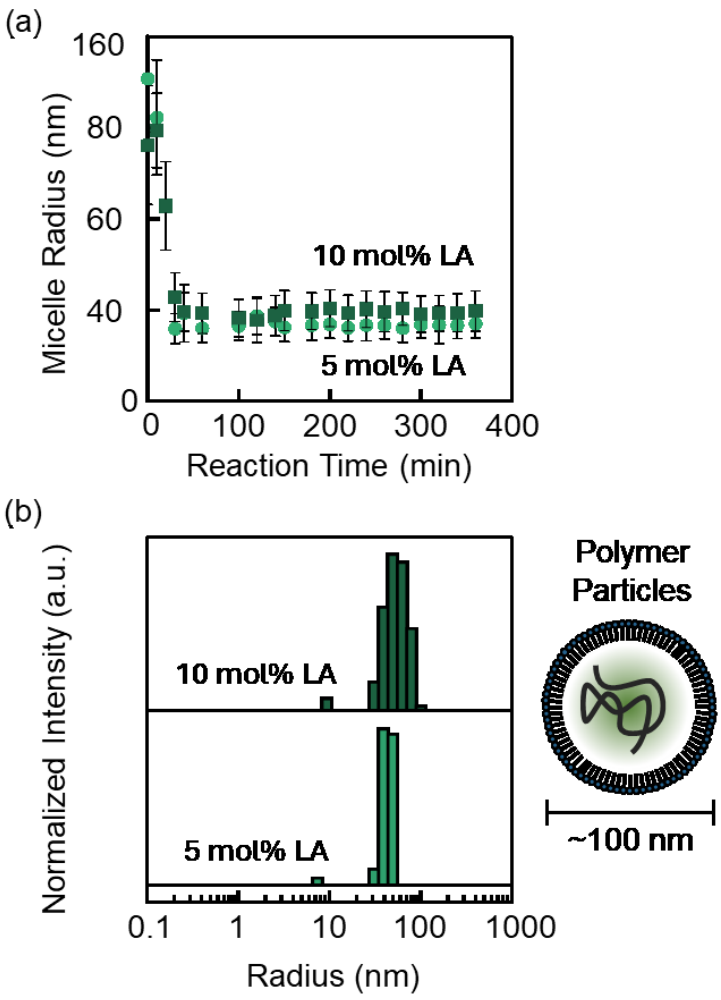

Figure 2. Dynamic light scattering (DLS) measurements of micelle size in each dispersion. **(a)** Average micelle size quickly decreases but remains stable for the duration of polymerizations with different loadings of α-lipoic acid (LA). Each time point is an average of 60 measurements collected from aliquots during polymerization. **(b)** The resulting polymer latexes have narrow size distributions and radii well below those required to be considered a miniemulsion (<250 nm).

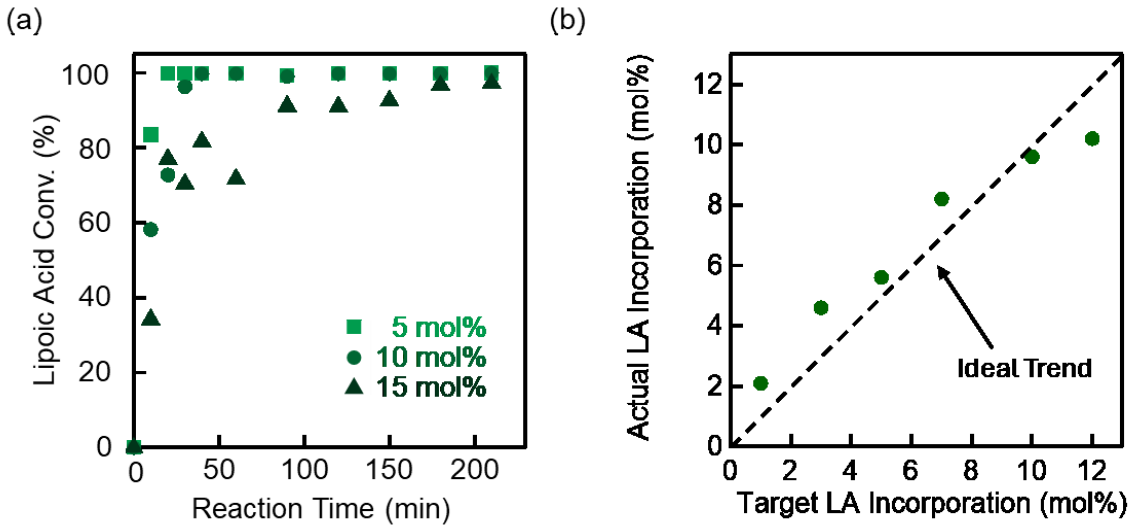

Figure 3. (a) Miniemulsion polymerizations with α-lipoic acid proceed rapidly. Note: At 15 mol% lipoic acid, some monomer remains insoluble and segregates as coagulum not accounted for by ^{1}H NMR spectroscopy. **(b)** At high monomer conversions, actual α-lipoic acid (LA) incorporation closely matches the feed composition plateauing at 10 mol%.

Given the efficacy of α-lipoic acid copolymerization in a miniemulsion setting and the ready availability of all starting materials, we sought to highlight the scalability of this reaction. To do so, a 4-liter aqueous emulsion containing 150 g of α-lipoic acid and 840 g of *n*-butyl acrylate was prepared in a 5-liter jacketed reaction flask equipped with an overhead stirrer as shown in **Figures 4a** and S11. The properties of this emulsion (20 wt% solids, avg. radius = 140 nm) were consistent with those previously created on a 10 mL scale. After polymerization, 622 g of polymer with M_n = 270 kg mol^{-1} and $Đ$ = 2.1 (**Figure 4b**) was isolated through direct precipitation of the aqueous phase into chilled methanol. These properties are similar to those achieved in batch, with marginally higher molecular weights attributed to the effects of compartmentalization and a molar-mass dispersity of ~2.0 as expected. Similarly, thermogravimetric analysis indicated the copolymer synthesized on a large scale (10 mol% α-lipoic acid) has a similar $T_{d5\%}$ as poly(*n*-butyl acrylate) synthesized in batch (230 °C vs. 250 °C respectively, Figure S12). Degradation with a solution of

tris(2-carboxyethyl)phosphine (10 eq. relative to the polymer disulfide content) in tetrahydrofuran/water (5/1 by weight) yielded a significant decrease in molar mass from 270 kg mol^{-1} to 20 kg mol^{-1}, which is due to cleavage of disulfide bonds along the polymer backbone (Figure S13). Despite the ease of degradation, the glass-transition temperature of *n*-butyl acrylate polymers containing *α*-lipoic acid remained nearly unchanged (Figure S14).

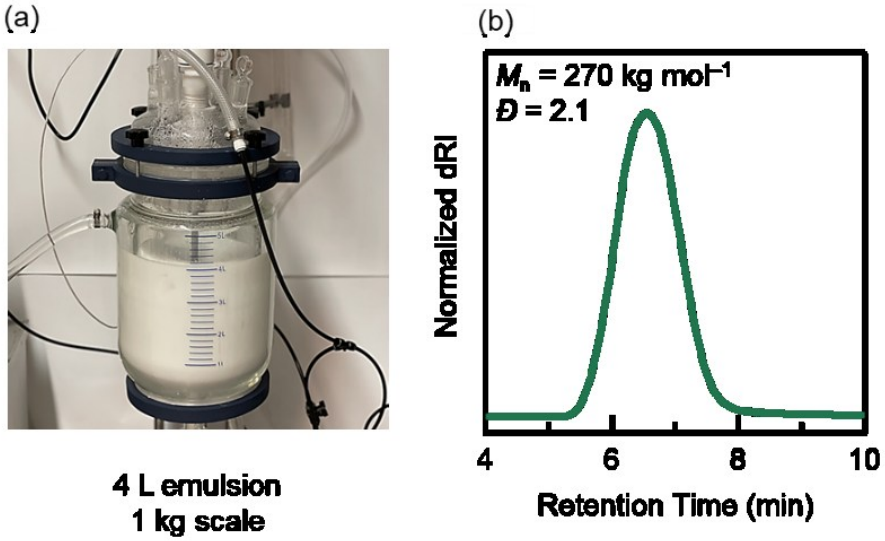

Figure 4. Large-scale aqueous miniemulsion copolymerization of *α*-lipoic acid (150 g) and *n*-butyl acrylate (840 g). **(a)** Photograph of the stable 4-liter latex after polymerization in a jacketed reaction vessel. **(b)** SEC of the isolated material indicates a high molecular weight (M_n = 270 kg mol^{-1}) and expected molar-mass dispersity ($Đ$ = 2.1).

With efficient emulsification conditions established for the copolymerization of *α*-lipoic acid and *n*-butyl acrylate, we next focused on monomer scope. To demonstrate the versatility of this strategy, a variety of comonomers having a range of properties was selected to highlight their solubility and emulsion stability with *α*-lipoic acid: styrene, trifluoroethyl acrylate, lauryl acrylate, ethylhexyl acrylate, and isobornyl acrylate. After preparing emulsions containing each monomer and ~10 mol% *α*-lipoic acid, copolymerization resulted in the formation of high molecular weight copolymers (>100 kg mol^{-1}) containing the targeted amount of lipoic acid as demonstrated by

methylation after purification (Figures S15–S19). Additionally, all of these copolymers were observed to degrade on demand when subjected to tris(2-carboxyethyl)phosphine (Figures S20–24).

Although the aforementioned solubility limit of *α*-lipoic acid (9.6 mol%) in *n*-butyl acrylate constrains the maximum content of degradable units, this limit is easily circumvented using a more oil-soluble dithiolane derivative. For example, in contrast to *α*-lipoic acid, ^{1}H NMR experiments indicated that ethyl lipoate is fully miscible with *n*-butyl acrylate (**Figure 5**).

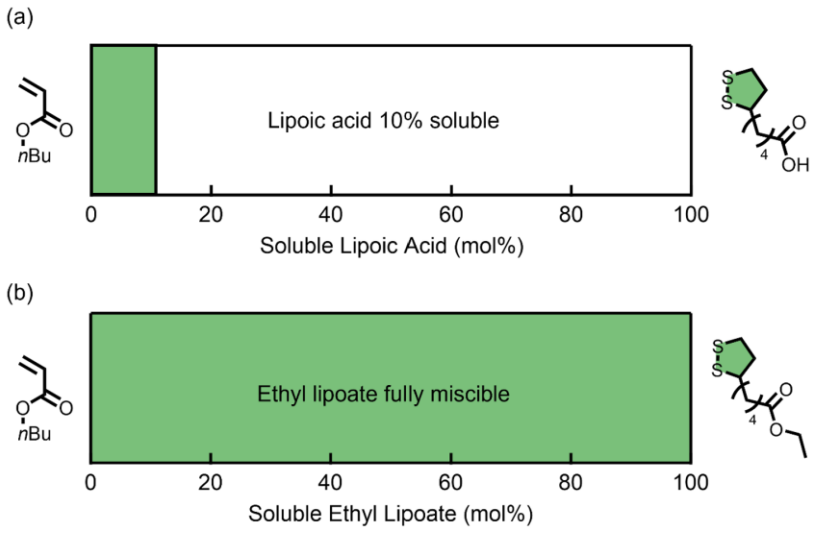

Figure 5. Comparing the solubility of dithiolanes in *n*-butyl acrylate as measured by ^{1}H-NMR spectroscopy. **(a)** The solubility limit of *α*-lipoic acid is 9.6 mol%. **(b)** In contrast, ethyl lipoate is fully miscible with *n*-butyl acrylate.

To take advantage of this enhanced miscibility, mixtures of ethyl lipoate and *n*-butyl acrylate were subjected to miniemulsification and subsequent polymerization, yielding polymers with molecular weights as high as 250 kg·mol^{-1} (**Figure 6**). Like emulsion copolymers with *α*-lipoic acid, measured compositions were reasonably consistent with the feed ratio of ethyl lipoate and high monomer conversion was achieved in all cases (Figures S25–S27). Encouragingly, each of these samples also undergoes a larger decrease in molar mass under reductive conditions than

the corresponding α-lipoic acid analogues (**Figures 6**). This trend is consistent with the total dithiolane content influencing molecular weight after degradation. (Note: because this system uses traditional free-radical polymerization, there will be a distribution of lengths generated between lipoate–lipoate diads as depicted by black lines of different lengths in **Figure 6**.) Similar to the aforementioned copolymers containing α-lipoic acid, the T_g of poly(*n*-butyl acrylate–*stat*–ethyl lipoate) remained essentially unchanged at all loadings up to 30 mol% (Figure S28). These results highlight the versatility of using various dithiolanes in scalable miniemulsion polymerizations that are commercially available or easy to access.

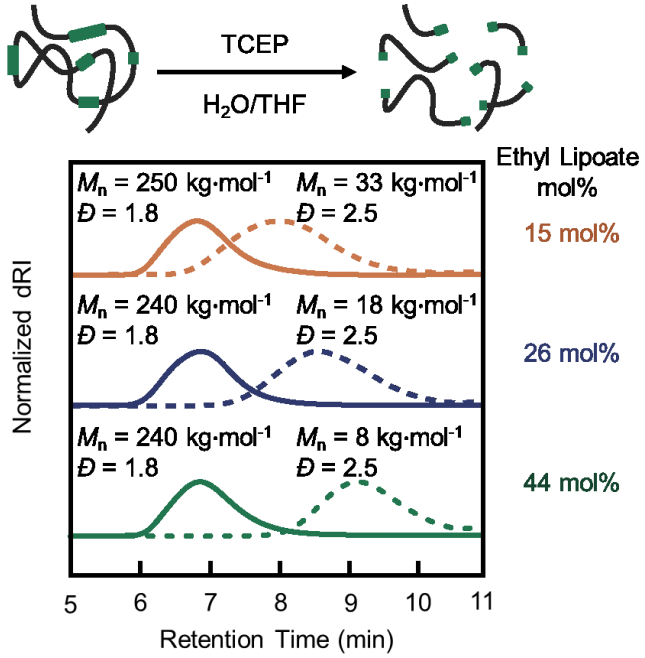

Figure 6. Copolymers containing ethyl lipoate degrade to lower molar masses than lipoic acid containing copolymers (8 kg mol^{-1} vs. 20 kg mol^{-1}, see SI for details). This result was achieved by surpassing the solubility limit of α-lipoic acid. Ethyl lipoate mol% is the actual content as measured by ^{1}H NMR spectroscopy after purification (see SI for details).

Conclusions

In summary, α-lipoic acid is compatible with miniemulsion copolymerization on a kilogram scale, yielding degradable copolymers with tunable properties and degradation profiles.

The use of sodium dodecylsulfate as a surfactant, azoisobutyronitrile as a radical initiator, and hexadecane as a costabilizer led to stable emulsions of *α*-lipoic acid and *n*-butyl acrylate in water. This simple procedure enabled polymerizations to be performed on a 4-liter scale, yielding high conversions, molecular weights (270 kg mol^{-1}), and tunable degradability depending on the content of *α*-lipoic acid. A solubility limit of ~10 mol% *α*-lipoic acid in *n*-butyl acrylate was readily circumvented by using ethyl lipoate—the ethyl ester of *α*-lipoic acid—which is fully miscible with *n*-butyl acrylate. These results demonstrate the versatility of using *α*-lipoic acid as a commercially available, biocompatible, and sustainable building block to create degradable polymers at scales difficult to access with other cyclic monomers that undergo radical ring-opening polymerization. We anticipate this simple and accessible strategy will be of interest to the broader materials community and beyond.

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Supporting Information

Reagent information, instrument specifications, synthetic procedures and experimental details, DLS data (Figures S1, S2), size-exclusion chromatograms (Figures S3, S13, S20–S24), ^{1}H NMR spectra and kinetic data derived therefrom (Figures S4–S8, S10, S15–S19, S26), photograph

of the jacketed reactor (Figure S11), thermogravimetric analysis (Figure S12), differential scanning calorimetry (Figures S14, S28).

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