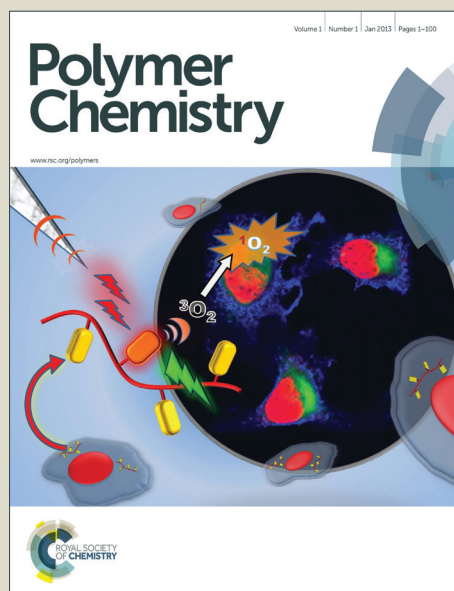


# Polymer Chemistry

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## ARTICLE

# Lipoates as Building Blocks of Sulfur-Containing Branched Macromolecules

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The radical copolymerization of cyclic disulfide-type monomers (ethyl lipoate or lipoic acid) with ethyl acrylate (1 : 1 molar feed ratio) yielded copolymers containing significant fraction of backbone disulfide groups, which were degradable upon reduction. A compound containing two-types of radically polymerizable groups (cyclic disulfide (1,2-dithiolane) and vinyl), 2-acryloyloxyethyl lipoate (AOELp), was synthesized and demonstrated to be a useful precursor of highly branched sulfur-containing polymers. Under radical polymerization conditions, AOELp served as a crosslinker, but up to moderate to high conversions and prior to gelation, soluble highly branched polymers were produced containing reductively degradable disulfide moieties, originating from the attack of sulfur-centered radical on a 1,2-dithiolane group from AOELp or the polymer (pendant group), or the coupling of two sulfur-centered radicals. Alternatively, the reduction of AOELp afforded the corresponding dithiol acrylate (an AB<sub>2</sub>-type monomer), which participated in radical or ionic step-growth thiol-ene reactions, yielding highly branched reductively non-degradable polymers with thioether-type sulfur atoms in the backbones.

## Introduction

Cyclic di-<sup>1-13</sup> and polysulfides<sup>14-18</sup> can participate in a variety of radical and ionic ring-opening reactions, redox processes, complexation with transition and main group metals and metal ions, etc., and their structure and reactivity have been the subject of many experimental and theoretical studies. A number of cyclic di- and polysulfides are well known natural products, e.g., lipoic and asparagusic acid, nereistoxin, charatoxin, brugine, gerrardine, etc., and their biological activity has further fuelled the interest in these compounds.<sup>19,20</sup> Lipoic acid (LpA), which contains a saturated five-membered disulfide ring (1,2-dithiolane) is perhaps the best known member of the group, which plays an important role as a coenzyme in biological redox processes, e.g., oxidative decarboxylation, and has found applications as an important antioxidant and dietary supplement.<sup>21-24</sup> In addition to its biological role, LpA and its reduced form, the dithiol dihydrolipoic (6,8-dimercaptooctanoic) acid, similar to other disulfides and thiols, have a marked affinity for precious (e.g., Au, Ag, Pd) and non-precious (e.g., Cr, Co, Ni) metals and metal ions (e.g., Cd<sup>2+</sup>, Zn<sup>2+</sup>). Because of this property, numerous polymeric materials have been developed that contain pendant lipoate moieties,<sup>25</sup> which have been successfully employed as adhesives for metals used in dentistry<sup>26,27</sup> or stabilizers and/or surface modifiers for the functionalization of metal, often Au,

nanoparticles,<sup>28,29</sup> and quantum dots.<sup>30</sup> Polymers with multiple pendant 1,2-dithiolane (including lipoate) groups can be reduced to macromolecular multithiols, which can be further oxidized, or participate in thiol-disulfide interchange with disulfides; both processes have been utilized in the preparation of micelles with disulfide-based crosslinked cores<sup>31</sup> or dynamic, self-healing, gels.<sup>32</sup>

The attack of anions or radicals on cyclic disulfides leads to opening of the disulfide-containing ring, yielding thiolate anions or sulfur-centered radicals, respectively, each one of which can initiate ring-opening oligomerization or polymerization reactions of the parent cyclic disulfide. Radical ring-opening polymerization<sup>33-37</sup> is a useful method for the synthesis of polymers with cleavable functionalities in the main chain such as ester,  $\alpha$ -ketoester, carbonate, amide, disulfide, carbon-carbon double bond, etc. Cyclic disulfides are of particular interest as monomers, since they yield polymers with backbone disulfide groups, which can be degraded chemically (upon either reduction or oxidation) or photochemically. The ability of cyclic disulfides to homopolymerize (affording linear polymers with multiple disulfide groups in the backbone) and to participate in copolymerization reactions with vinyl monomers, usually upon heating or irradiation, was established in the 1950s.<sup>38-44</sup> The propensities of cyclic disulfides to polymerize via ring-opening and of disulfide-containing polymers to depolymerize to the corresponding cyclic disulfides<sup>45,46</sup> are related to the ring strain and many attempts have been made to determine experimentally or estimate computationally this important structural parameter.<sup>40,46-49</sup> The formation of linear and cyclic (including catenane-type) disulfide-containing polymers derived from the six-membered heterocyclic compound 1,2-dithiane<sup>50-52</sup> and its derivative with a fused benzene ring<sup>53</sup> as well as from LpA<sup>54</sup> and its derivatives<sup>55,56</sup> has been extensively studied due to the interesting

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mechanical properties as well as the degradability of these materials. Owing to the unique ability of cyclic disulfides to participate in both radical and ionic ring-opening reactions, and that of the respectively formed sulfur-centered radicals or anions to either open another unreacted cyclic disulfide or add to a carbon-carbon double bond, it was envisioned that compounds containing both a cyclic disulfide and a reactive vinyl group would be suitable precursors of various highly branched (and – at high conversions – network) polymers.

(Hyper)branched polymers<sup>57-61</sup> have found numerous applications due to their properties, including low melt or solution viscosity compared to their linear counterparts of the same molecular weight, high degree of functionalization (and the presence of multiple branching point and chain end functionalities), etc., and development of methodologies for their synthesis is of great interest in fundamental and applied materials science, and industry. The classical synthetic routes to highly branched polymers included the step-growth polymerization of  $AB_x$  ( $x \geq 2$ ) or mixtures of  $A_2$  and  $B_x$  ( $x \geq 3$ ) monomers (in the latter case, gels are eventually formed). In addition, chain-growth polymerization methods have been developed, including the “self-condensing” polymerization of compounds with initiating and polymerizable groups (inimers),<sup>62</sup> or the copolymerization of mono- and di- or polyfunctional monomers in the presence of compounds able to limit the molecular weights of the polymers (transfer agents, reagents capable of reversibly capping or deactivating the propagating centers, or excess of radical sources) and thus – of delaying gelation.

Herein, it is demonstrated that the compound 2-acryloyloxyethyl lipoate (AOELp), which contains two types of radically polymerizable groups (vinyl and 1,2-dithiolane) can be successfully employed in the synthesis of sulfur-containing highly branched polymers, which, depending on the polymerization conditions, can be degradable or stable in the presence of reducing agents. Under conventional radical polymerization conditions, AOELp affords highly branched polymers with backbone thioether and disulfide groups, the latter originating from at least two successive additions of a propagating radical to 1,2-dithiolane groups from the monomer or polymer, and making the polymers partially degradable upon reduction. In this case the compound serves as a crosslinker and highly branched polymers are obtained up to moderate conversions but eventually gelation occurs. When AOELp is first reduced to the corresponding dithiol and then reacted with bases or radical sources, efficient thiol-ene reactions<sup>63-66</sup> take place and lead to the formation of highly branched polymers containing virtually exclusively thioether-type sulfur atoms in the backbone, which are stable towards reducing agents. In this case, the reduced compound is an  $AB_2$ -type monomer that participates in step-growth polymerization.

## Experimental Section

### Materials

Lipoic acid (LpA, 98 %, Acros), 2-hydroxyethyl acrylate (HEA, 96 %, Aldrich), *N,N'*-dicyclohexylcarbodiimide (DCC, 99 %, Aldrich), 4-(*N,N*-dimethylamino)pyridine (DMAP, 99 %, Aldrich), azobisisobutyronitrile (AIBN, 98 %, Aldrich), 2,2-

dimethoxy-2-phenyl-acetophenone (DPAP, 99 %, Aldrich), tributylphosphine ( $Bu_3P$ , 95 %, Alfa Aesar), 2-mercaptoethanol (98 %, Bio-Rad), dithiothreitol (DTT, 99 %, Gold Bio Tech),  $NaBH_4$  (98 %, Acros), Zn dust ( $<10 \mu m$ ,  $\geq 98$  %, Aldrich), aqueous hydrochloric acid (37 %, BDH), and trimethylsilyl diazomethane (TMSDAM, 2 M in ether, Acros) were used as received. Ethyl acrylate (EA, 99%, Acros) was purified by passing the neat liquid through a column filled with basic alumina to remove the polymerization inhibitor. The deuterated solvents ( $CDCl_3$  (99.8 % D),  $CD_3CN$  (99.8 % D), and acetone- $d_6$  (99.9 % D)) were purchased from Cambridge Isotope Laboratories; a small amount of tetramethylsilane (TMS) was added to them as a chemical shift reference. *N,N*-dimethylacetamide (DMAc, 99 %, Acros), tetrahydrofuran (THF, 99 %, Fisher), and benzonitrile (99 %, Acros) were dried with anhydrous sodium sulfate powder for at least 12 h prior to use. All other solvents were used as received without further treatment.

### Analyses and equipment

Molecular weights and molecular weight distribution dispersities ( $M_w/M_n$ ) were determined by size exclusion chromatography (SEC) on a Tosoh EcoSEC system equipped with a series of 4 columns (TSK gel guard Super HZ-L, Super HZM-M, Super HZM-N, and Super HZ2000) and using refractive index (RI) and UV detectors. THF was used as the eluent at a flow rate of  $0.35 \text{ mL min}^{-1}$  (40 °C). The SEC calibration was based on linear polystyrene standards. Monomer conversions were determined by  $^1H$  NMR spectroscopy using a Bruker Avance DRX 400 or a JEOL ECA 500 MHz spectrometer. The UV bench lamp (UVP XX-20S) was equipped with two Hg lamps (254 nm, 20 W).

### Synthetic procedures

**Synthesis of 2-acryloyloxyethyl lipoate (AOELp).** LpA (5.000 g, 0.024 mol) and HEA (3.0 mL, 0.026 mol) were dissolved in THF (30 mL) in a 100-mL round bottom flask equipped with a magnetic stir bar. The solution was cooled in an ice bath and a solution of DCC (5.000 g, 0.024 mol) in THF (10 mL) was added, followed by DMAP (0.586 g, 0.0048 mol). The flask was capped with a rubber septum and the mixture was stirred in the cooling bath for 1 h. Then, the reaction was stirred at room temperature (r.t.) for additional 20 h. The precipitated dicyclohexylurea was filtered off and washed with three 20-mL portions of THF. The solvent was removed from the combined filtered reaction mixture and washing liquid on a rotary evaporator yielding the crude lipoate ester as a yellow oil. The product was dissolved in 50 mL of  $CH_2Cl_2$ , washed with de-ionized water ( $2 \times 30 \text{ mL}$ ), 5 % aqueous solution of NaOH ( $2 \times 30 \text{ mL}$ ), de-ionized water ( $2 \times 30 \text{ mL}$ ), 1 M aqueous HCl ( $2 \times 30 \text{ mL}$ ), and again, with de-ionized water ( $2 \times 30 \text{ mL}$ ). The organic phase was collected and dried over anhydrous  $Na_2SO_4$ . The solvent was removed on a rotary evaporator to afford the final product. The yield was 3.98 g (54.5 %).  $^1H$  NMR (500 MHz,  $CDCl_3$ ,  $\delta$ ): 6.41 (dd, 1H), 6.14 (dd, 1H), 5.86 (dd, 1H), 4.34 (m,

4H), 3.55 (m, 1H), 3.17 (m, 1H), 3.11 (m, 1H), 2.45 (m, 1H), 2.35 (t, 2H), 1.90 (m, 1H), 1.68 (m, 4H), 1.47 (m, 2H).

**Synthesis of ethyl lipate (ELp).** LpA (2.063 g, 0.01 mol) and anhydrous ethanol (2.92 mL, 0.05 mol) were dissolved in THF (15 mL) in a 50-mL round bottom flask equipped with a magnetic stir bar. The solution was cooled in an ice bath and a solution of DCC (2.063 g, 0.01 mol) THF (10 mL) was added, followed by a solution of DMAP (0.244 g, 0.002 mol in 5 mL of THF). The flask was capped with a rubber septum and the mixture was stirred in the cooling bath for 1 h. Then, the reaction was stirred at r.t. for additional 20 h. The precipitated dicyclohexylurea was filtered off and washed with three 20-mL portions of THF. The solvent was removed from the combined filtered reaction mixture and washing liquid on a rotary evaporator yielding the crude lipate ester as a yellow oil. The product was dissolved in 25 mL of  $\text{CH}_2\text{Cl}_2$ , washed with de-ionized water ( $2 \times 30$  mL), 5 % aqueous solution of NaOH ( $2 \times 30$  mL), de-ionized water ( $2 \times 30$  mL), 1 M aqueous HCl ( $2 \times 30$  mL), and again, with de-ionized water ( $2 \times 30$  mL). The organic phase was collected and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . The solvent was removed on a rotary evaporator to afford the product (1.920 g). The product was dissolved in 2 mL of dry THF and stored in a freezer ( $-18^\circ\text{C}$ ) overnight and the white precipitated DCU was filtered off. The solvent was removed again under vacuum to yield the final product (1.151 g, 49.1 %).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 4.13 (q, 2H), 3.56 (m, 1H), 3.17 (m, 1H), 3.13 (m, 1H), 2.45 (m, 1H), 2.31 (t, 2H), 1.90 (m, 1H), 1.68 (m, 4H), 1.47 (m, 2H), 1.25 (t, 3H).

**Copolymerization of ELp and EA.** AIBN ( $0.003$  g,  $1.64 \times 10^{-5}$  mol), ELp ( $0.385$  g,  $1.64 \times 10^{-3}$  mol) and EA ( $0.18$  mL,  $1.64 \times 10^{-3}$  mol) were dissolved in DMAc (1 mL) in a reaction tube, to which a magnetic stir bar had been added. Benzonitrile (0.05 mL) was then added as internal standard for calculation of the monomer conversion by  $^1\text{H}$  NMR spectroscopy. The tube was capped with a rubber septum, immersed in an ice bath, and the mixture was purged with nitrogen for 30 min, after which the tube was transferred into an oil bath preheated to  $65^\circ\text{C}$  to start the polymerization. Samples (ca. 0.02 mL) were periodically withdrawn with a nitrogen-purged syringe to monitor the monomer conversion ( $^1\text{H}$  NMR) and the apparent molecular weights and molecular weight distributions of the polymers (SEC). After 24 h, the reaction mixture was dialyzed against methanol for 2 days (using a dialysis membrane with cut-off molecular weight of a 2,000 Da), during which period the solvent was regularly changed with fresh solvent. The solvent was then removed from the purified polymer solution on a rotary evaporator to yield the final copolymer polyELp-copolyEA (0.092 g). Copolymerizations of LpA with EA were also carried out as described in the Supporting information.

**Synthesis of branched polymers derived from AOELp by free radical polymerization.** First, a stock solution of AIBN ( $0.013$  g,  $8.2 \times 10^{-5}$  mol) in DMAc (5 mL) was prepared ( $1.64 \times 10^{-5}$  mol  $\text{mL}^{-1}$ ). AOELp ( $0.200$  g,  $6.57 \times 10^{-4}$  mol) was added to 0.4 mL of the above stock solution in a reaction tube (the molar ratio of

radical initiator to monomer was 1 : 100), in which a magnetic stir bar had been inserted. One drop of benzonitrile was added as internal standard in order to calculate the conversion by  $^1\text{H}$  NMR spectroscopy. The tube was capped with a rubber septum, immersed in an ice bath, and the mixture was purged with nitrogen for 30 min. The reaction tube was then transferred into an oil bath preheated to  $65^\circ\text{C}$  to start the polymerization. Samples (ca. 0.02 mL) were periodically withdrawn with a nitrogen-purged syringe to monitor the monomer conversion and the apparent molecular weights and molecular weight distributions of the polymers. At these conditions, crosslinking was observed after ca. 6 h. Similar reactions were carried out using smaller amounts of AIBN (0.2 mL of the above AIBN stock solution and 0.2 mL of pure DMAc to achieve  $[\text{AOELp}]_0 : [\text{AIBN}]_0 = 200 : 1$ , and 0.1 mL of stock solution and 0.3 mL of pure DMAc for  $[\text{AOELp}]_0 : [\text{AIBN}]_0 = 400 : 1$ ). Gelation was observed again but after ca. 18 h and 50 h in the reactions with  $[\text{AOELp}]_0 : [\text{AIBN}]_0 = 200 : 1$  and  $400 : 1$ , respectively.

**NMR studies of reduction of AOELp.** AOELp ( $0.121$  g,  $3.98 \times 10^{-4}$  mol) was dissolved in  $\text{CD}_3\text{CN}$  (1 mL) in a vial equipped with a magnetic stir bar and aqueous solution of HCl (37 %, 0.13 mL,  $1.6 \times 10^{-3}$  mol) was added. A small sample ( $< 0.05$  mL) was taken, diluted with  $\text{CD}_3\text{CN}$ , an  $^1\text{H}$  NMR spectrum was collected. Then, Zn dust ( $0.039$  g,  $5.97 \times 10^{-4}$  mol) was added to the reaction mixture and it was stirred at r.t. During the reaction, small samples ( $< 0.05$  mL) were withdrawn to monitor the reductive opening of the 5-membered disulfide-containing ring to the corresponding dithiol by  $^1\text{H}$  NMR spectroscopy. Based on NMR analysis, the reaction was complete within 5 min, but the stirring was continued for 1 h before the next steps were undertaken.

**Reduction of AOELp followed by thiol-ene click reactions.** (i) The solution containing reduced AOELp in  $\text{CD}_3\text{CN}$  described above was mixed with  $\text{CH}_2\text{Cl}_2$  (15 mL) and the  $\text{ZnCl}_2$  and HCl present in the mixture were extracted with deionized water ( $3 \times 10$  mL). The organic phase was collected and dried over anhydrous  $\text{Na}_2\text{SO}_4$  and the solvent was removed on a rotary evaporator to afford the final product of reduction ( $0.074$  g,  $2.42 \times 10^{-4}$  mol), which was kept in a glass tube under nitrogen to prevent oxidation. Separately, a solution of DPAP ( $0.006$  g,  $2.42 \times 10^{-5}$  mol) in benzonitrile (1 mL) was prepared and was added, along with a magnetic stir bar, under nitrogen atmosphere to the test tube containing the dithiol. The tube was sealed with a rubber septum and the reaction mixture was stirred at r.t. under UV irradiation. Samples were periodically withdrawn with a nitrogen-purged syringe for  $^1\text{H}$  NMR and SEC analysis. After 10 h, the polymer in the remaining solution was precipitated in methanol and dried. (ii) Another reduction was carried out that employed  $\text{NaBH}_4$ . AOELp ( $0.400$  g,  $1.31 \times 10^{-3}$  mol) was dissolved in THF (2 mL) and  $\text{NaBH}_4$  ( $0.075$  g,  $1.97 \times 10^{-3}$  mol) was added slowly. The mixture was stirred at r.t. for 3 h. All insoluble solids were filtered off and the product was characterized by  $^1\text{H}$  NMR spectroscopy after filtration and

dilution with  $\text{CDCl}_3$ , and SEC after filtration and dilution with THF.

## Results and discussion

### Copolymerization of AOELp with acrylates

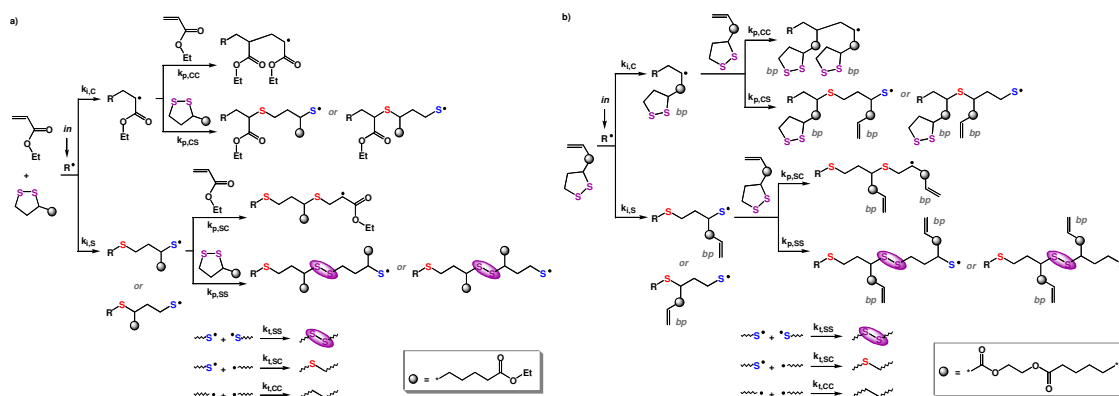
The ring-opening homopolymerization of LpA or its derivatives (e.g., amides) yields polymers with multiple disulfide groups in the backbone. When these cyclic disulfide monomers are copolymerized with vinyl monomers, the produced polymers may contain a significant fraction of backbone disulfide or thioether groups, depending on the feed ratios of the comonomers and their reactivities. For example, the reaction steps involved in the copolymerization of ELP and EA are presented in Scheme 1a ( $k_{i,X}$  ( $k_{i,Y}$ ),  $k_{p,XY}$ , and  $k_{t,XY}$ , where X and Y represent C and/or S, are respectively the initiation, propagation, and termination rate coefficients for reactions generating an X- or Y-centered propagating radical (initiation), reactions involving a X-centered radical to produce a Y-centered one (propagation), or coupling of an X- with a Y-centered radical (termination)), which shows that backbone disulfide groups could only be formed by at least two sequential ring opening reactions of the 1,2-dithiolane-based monomer ( $k_{p,SS}$ ) or by radical coupling of two propagating sulfur-centered radicals ( $k_{t,SS}$ ).

A derivative of LpA, lipoamide, has been shown to copolymerize with various vinyl monomers, and it was ascertained that under identical reaction conditions, the amount of incorporated lipoamide in the copolymer increased as the vinyl comonomer was altered in the order: methyl methacrylate << styrene ≤ acrylonitrile < methyl acrylate <

vinyl acetate.<sup>67</sup> Since one of the purposes of this study was to develop methods for the synthesis of partially reductively degradable (disulfide-containing) branched polymers, it was important to select a monomer with a vinyl moiety, which forms radicals that are sufficiently reactive towards 1,2-dithiolanes. Based on the above-mentioned study, acrylates were markedly better candidates than methacrylates. Indeed, ELP could be successfully copolymerized with EA using AIBN as the radical source (Figure 1a). The presence of sequential ELP-derived monomer units (i.e., the presence of disulfide groups) in poly(ELP-co-EA), produced using a feed molar ratio of 1 : 1, could be demonstrated easily by adding a strong reducing agent,  $\text{Bu}_3\text{P}$ ,<sup>68</sup> to solutions of the polymers and conducting SEC analyses (Figure 1b); the molecular weight of the copolymers decreased markedly after treatment with the reducing agent.

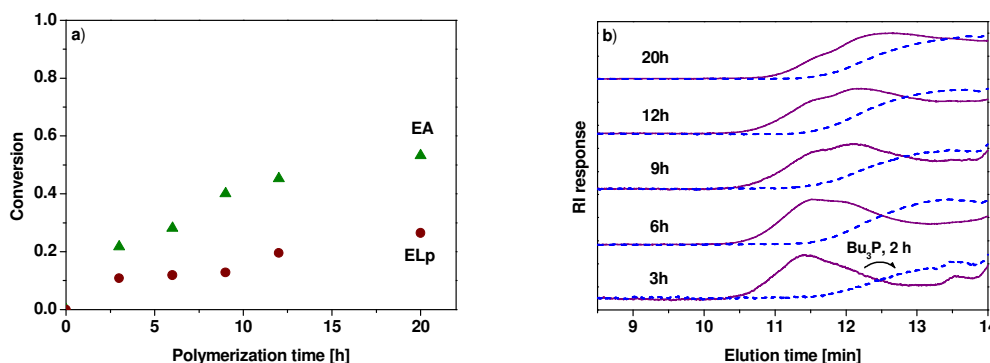
Similar to ELP, the parent acid (LpA) could also be successfully copolymerized with the acrylate monomer EA (Figure S1). In order to characterize the copolymer of LpA and EA and study its reduction by SEC, the possibility of potential interactions of the pendant carboxylic acid groups with the material of the beads in the SEC columns had to be eliminated. This was accomplished by methylation of the carboxylic acid groups to the corresponding methyl ester (Figure S2) prior to the analyses. As Figure S3 demonstrates, the copolymers formed in the copolymerization LpA and EA (feed molar ratio of 1:1) contained a significant amount of backbone disulfide links.

These studies indicated that AOELp, a monomer containing two different radically polymerizable groups (1,2-dithiolane and vinyl) could be employed for the formation of partially degradable highly branched polymers and eventually (at high monomer conversions) partially degradable network polymers. The main elementary reactions taking place in the radical polymerization of AOELp are presented in Scheme 1b.



**Scheme 1** a) Main reaction steps in the copolymerization of EA and ELP, leading to the formation of partially reductively degradable (disulfide-containing) polymers; and b) Homopolymerization of AOELp leading to partially reductively degradable highly branched polymers. The branching points are designated as *bp* and the disulfide bonds, which are responsible for the degradability, are highlighted.





**Fig. 1** a) Kinetics of radical copolymerization of ELP and EA initiated by AIBN at 65 °C in DMAc and b) Evolution of SEC traces of the copolymers (solid lines) and the products of their reductive degradation upon addition of Bu<sub>3</sub>P (20 µL to a solution of 5 mg of copolymer in 1 mL of THF) after 2 h (dashed lines).

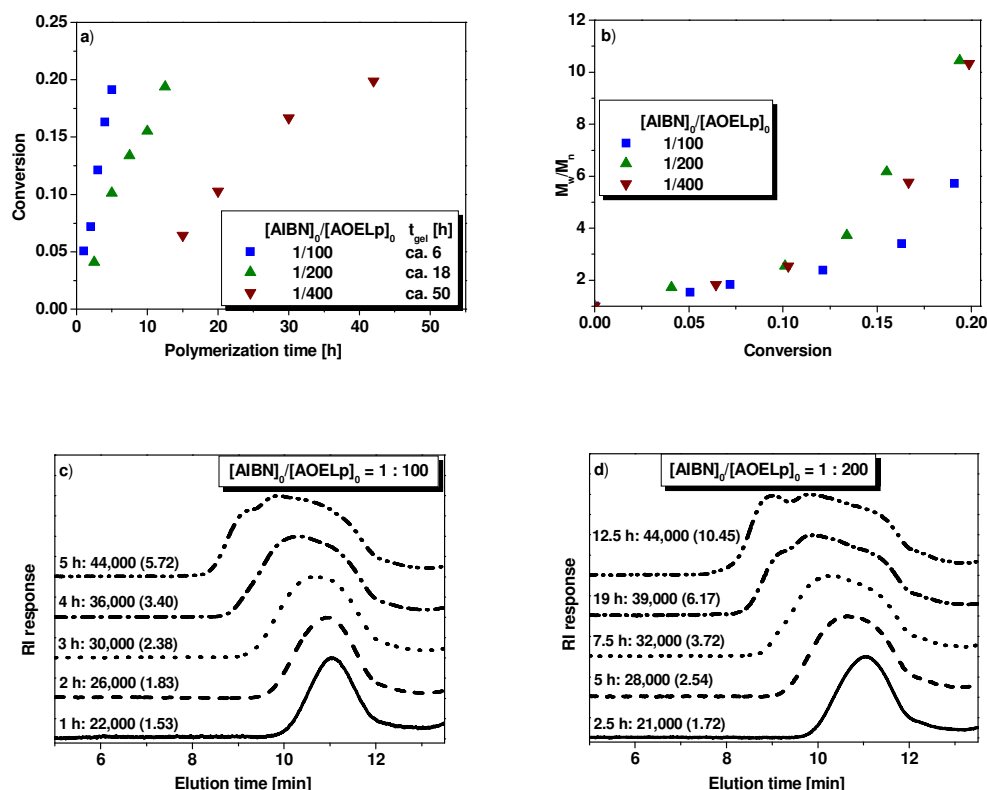
#### Preparation of highly branched disulfide-containing polymers via radical polymerization of AOELp

Branched polymers containing reductively degradable disulfide functionalities at all or some of the branching points have numerous potential applications as dynamic materials (due to their ability to participate in thiol-disulfide interchange reactions) and in the biomedical field, and this has been a major driving force for the development of procedures for their synthesis. Of the chain growth methods, self-condensing radical homo- and copolymerizations employing a disulfide-based methacrylate inimer containing an alkyl bromide-type moiety, able to initiate atom transfer radical polymerization (ATRP<sup>69-71</sup>), have been reported.<sup>72,73</sup> The main disadvantage of the procedure is the use of difficult to synthesize inimers. In addition, the polymerization of disulfide-containing divinyl crosslinkers under ATRP conditions<sup>74</sup> or in the presence of efficient chain transfer agents, e.g., CBr<sub>4</sub>,<sup>75,76</sup> have also been successfully used to prepare various disulfide-containing highly branched polymers. Herein, we report on the use of application of AOELp (a type of crosslinker with two polymerizable moieties with different reactivities) for the synthesis of highly branched polymers.

AOELp was successfully prepared via the DCC-mediated and DMAP-catalyzed esterification of LpA with a common hydrophilic monomer, 2-hydroxyethyl acrylate. The homopolymerization of AOELp initiated by AIBN in DMAc at 65 °C yielded soluble highly branched polymers up to about 20 % conversion (Figure 2), at which point macroscopic gelation was observed. The ratios of radical initiator to monomer/crosslinker (AOELp) were varied from 1 : 400 to 1 : 100 and, as expected, the initiator concentration affected the

polymerization rate and the time, at which gelation occurred ( $t_{gel}$ ), but had no significant effect on the conversion, at which network polymers were formed. As the reactions proceeded and prior to gelation, the viscosity visibly increased and the molecular weight distributions (MWDs) of the polymers broadened. This suggested that the branching degree of the polymers increased with conversion, and, based on the values of weight- to number-average molecular weights ( $M_w/M_n$ ; Figure 2b) and, more importantly – on the shapes of the MWDs (Figures 2c and 2d), was somewhat lower for the reaction with the largest amount of AIBN. For instance, at ca. 20 % monomer/crosslinker conversion, the  $M_w/M_n$  values of the soluble polymers were 5.72, 10.45, and 10.34 for the systems using AIBN amounts of 1 : 100, 1 : 200, and 1 : 400 vs. AOELp, respectively).

The results from the copolymerizations of ELP and EA (at molar ratio of 1 : 1, which is the same as the molar ratio of the two polymerizable groups (1,2-dithiolane and vinyl) in AOELp) suggested that the soluble highly branched polymers should contain a significant fraction of backbone disulfide groups and should be degradable upon reduction. At the same time, as shown in Scheme 1b, the branched polymers should contain a large number of pendant cyclic disulfide and vinyl groups. To induce the reductive cleavage of the backbone disulfide groups in the branched polymers, the samples were treated with various reducing agents – from the relatively weakly/slowly reducing DTT (Cleland's reagent<sup>77</sup>) and 2-mercaptoethanol to the more reactive Bu<sub>3</sub>P. The SEC traces of a polymer from the reaction mixture using a molar ratio of AIBN to AOELp of 1 : 100 at ca. 20 % conversion (i.e., just prior to gelation) before and 10 h after treatment with the mentioned reducing agents at r.t. in THF are presented in Figure 3.

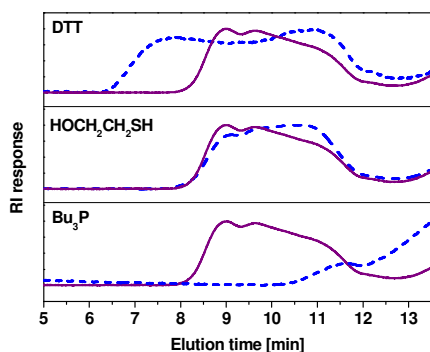


**Fig. 2** Polymerization of AOELp with different amounts of initiator (AIBN) in DMAc at 65 °C: a) kinetics and approximate gelation time ( $t_{\text{gel}}$ ), and b) evolution of MWD dispersity ( $M_w/M_n$ ) with monomer conversion for each reaction; c) and d) SEC traces of the polymers obtained at different conversions for the reactions using  $[AIBN]_0/[AOELP]_0 = 1 : 100$  and  $1 : 200$ , respectively (the polymerization time, the SEC-based  $M_n$  [g mol<sup>-1</sup>], and the values of  $M_w/M_n$  (in parentheses) are shown at each curve).

In the presence of DTT, a small part of the polymer degraded, but a relatively large fraction of polymer with higher molecular weight than the starting branched polymer was produced. A plausible explanation is that DTT, a dithiol, can react not only with the backbone disulfide groups and cleave them, but can also participate in thiol-ene reactions with the numerous pendant acrylate groups, in which case it would serve as a thioether-forming linker between branched molecules. A monothiol, 2-mercaptoethanol, can also participate in disulfide reduction and thiol-ene addition, but cannot act as a crosslinker, which was indeed observed (note the formation of small amount of low molecular weight polymer but the absence of high molecular weight product of partial crosslinking). Clearly, although some reduction took place upon treatment with thiols, the polymer degradation was not very pronounced. However, when Bu<sub>3</sub>P was employed, the apparent molecular weight of the polymer decreased rather drastically, proving that the fraction of backbone disulfide bonds in the branched polymer was significant. The highly branched disulfide (DS)-containing polymers prepared by radical polymerization of AOELp will be designated as *hb*-polyAOELp<sup>DS</sup> to distinguish them from the polymers prepared from AOELp in the presence of reducing

agents (*vide infra*), in which the backbone sulfur atoms are exclusively in the form of thioether (TE) groups, and which will be named *hb*-polyAOELp<sup>TE</sup>.

It should be noted that Bu<sub>3</sub>P can also add to the pendant acrylate-type vinyl bonds (Michael addition), with the formation of phosphonium pendant groups. This reaction may contribute to the observed very low apparent molecular weight because THF (the SEC eluent) is likely a poor solvent for polymers with multiple ionic functional groups and the phosphonium-containing macromolecules may be in a partially collapsed state. To ascertain whether Bu<sub>3</sub>P is sufficiently reactive towards acrylates, a model reaction between this phosphine and EA was studied by means of <sup>1</sup>H NMR spectroscopy (Figure S4). Within several minutes the Michael addition was complete in CDCl<sub>3</sub> at r.t.

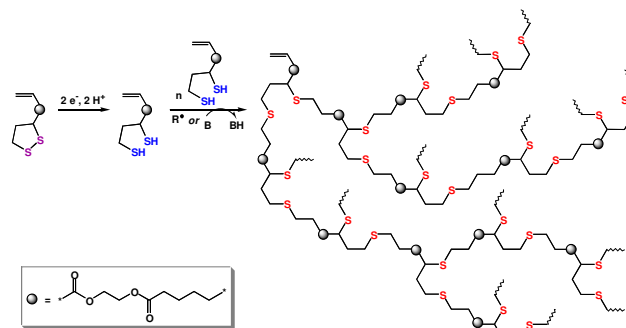


**Fig. 3** SEC traces of a highly branched polymer obtained by the radical polymerization of AOELp (using ratio of AIBN to AOELp of 1 : 100 at ca. 20 % monomer conversion; solid lines) and the products of its reaction with DTT, mercaptoethanol, and Bu<sub>3</sub>P (dash lines). All reductions were carried out for 10 h at r.t. in THF.

#### Preparation of highly branched non-degradable polymers by thiol-ene click reactions involving AOELp

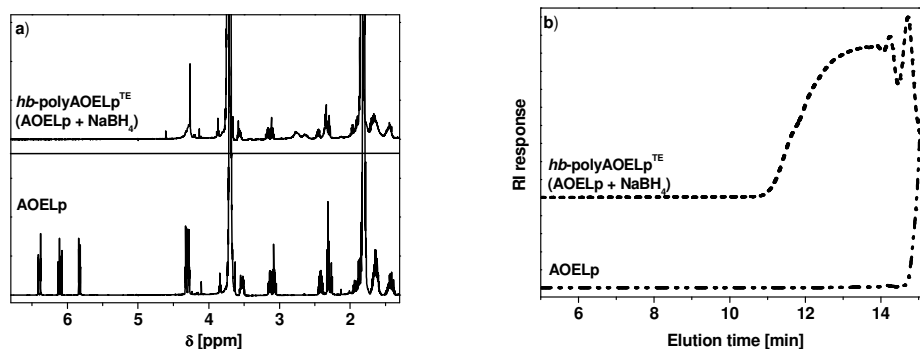
Disulfides RS<sub>2</sub>R are redox-active compounds and their reduction leads to the formation of thiolates RS<sup>-</sup> or thiols RSH, depending on pH of the reaction system and/or the nature of the reducing agent. Various reducing agents have been used for the reduction of disulfides to thiol(ates), including metal hydrides (e.g., NaBH<sub>4</sub>), phosphines (e.g., Bu<sub>3</sub>P), thiols (e.g., mercaptoethanol and DTT), metal/acid combinations (e.g., Zn and HCl), etc.<sup>78</sup> AOELp contains a cyclic disulfide group and its reduction affords an acrylate containing two thiol(ate) groups, in other words, a compound containing both functionalities participating in thiol-ene reactions. The thiol-ene click reaction

is an example of a high-yield coupling reaction, which has been widely used in the synthesis of various macromolecules,<sup>63-66</sup> and it was envisioned that the reduced AOELp could serve as an AB<sub>2</sub>-type monomer, the thiol-ene self-coupling of which would afford highly branched thioether-containing polymers (Scheme 2).



**Scheme 2** Formation of highly branched thioether-based polymers (polyAELpTE) via base-catalyzed or radical thiol-ene self-coupling of reduced AOELp.

As shown in Figure 4, when AOELp was reacted with a basic reducing agent, NaBH<sub>4</sub> in THF at r.t., the reduction of the 1,2-dithiolane cycle was immediately followed by base-catalyzed thiol-ene self-coupling (Michael addition) and highly branched polymer was formed *in situ*. The intermediate reactive molecule (reduced AOELp) could not be seen in the NMR spectra of samples taken from the reaction mixture, but the formation of the branched polymer was indicated both by NMR spectroscopy (Figure 4a; note the absence of signals corresponding to vinyl protons) and SEC analysis (Figure 4b).



**Fig. 4** a) <sup>1</sup>H NMR spectra (in CDCl<sub>3</sub>) of AOELp and the polymer produced by its reduction by NaBH<sub>4</sub> in THF at r.t. in 3 h. b) SEC traces of AOELp before and after reduction with NaBH<sub>4</sub>.

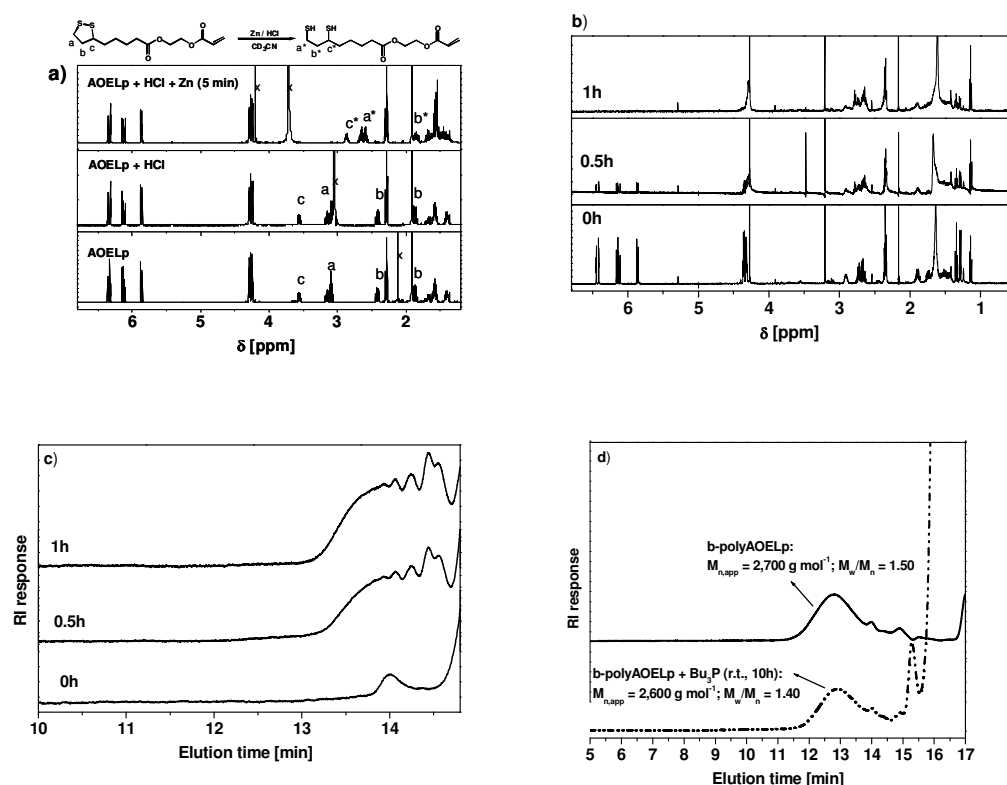
The performance of Bu<sub>3</sub>P and DTT as reducing agents was unsatisfactory, for they either participated in side reactions

(addition to the acrylate moiety, as discussed above and demonstrated in Figure S4) and/or were not able to efficiently reduce cyclic disulfides. However, when Zn and HCl were



employed, the reduction was complete, no side reactions were detected, and the dithiol (reduced AOELp) could actually be

isolated.



**Fig. 5** a)  $^1\text{H}$  NMR spectra (in  $\text{CD}_3\text{CN}$ ) of AOELp alone or in the presence of HCl, and the product of its reduction with Zn/HCl for 5 min. b)  $^1\text{H}$  NMR spectra of reduced AOELp and the branched polymers produced from it in the presence of radical photoinitiator (DPAP) under irradiation with UV light. c) SEC traces of AOELp reduced by Zn / HCl before and after radical thiol-ene reaction. d) SEC traces of the branched product of thiol-ene reaction before and after addition of a strong reducing agent ( $\text{Bu}_3\text{P}$ ).

As Figure 5a shows, the reduction was complete within minutes and the vinyl groups remained intact. Thiol-ene reactions could be performed in the same reaction tube, by simple addition of a radical source such as the thermal radical initiator AIBN or the photoinitiator DPAP and heating or irradiating the reaction mixture. Alternatively, the reduced AOELp could be isolated (while taking care to avoid oxidation, which would lead to the formation of the starting material, AOELp, or di-, oligo-, or even polymeric products of oxidative thiol coupling) and then reacted with radical initiators. The thermal reaction with AIBN (5 or 10 mol % vs. reduced AOELp,  $60^\circ\text{C}$ ) afforded branched polymers, but was relatively slow. When a photoinitiator was employed as the radical source and the reaction mixture was irradiated with intense UV light, the radical self-coupling was complete within 1 h (Figure 5b; observe the decrease of the intensity and the eventual disappearance of the signals of the vinyl protons as the reaction progressed). The formation of a branched polymer was also demonstrated by SEC analysis (Figure 5c). As expected,

based on the mechanism of polymer formation, the highly branched polymer was not degradable upon reduction due to the absence of disulfide bonds in the backbone (Figure 5d).

## Conclusions

Both lipoic acid and its esters could be efficiently copolymerized with acrylates under radical polymerization conditions, and the produced copolymers contained significant fraction of reductively degradable disulfide groups. A difunctional monomer/crosslinker containing a 5-membered cyclic disulfide (1,2-dithiolane) and a vinyl group, 2-acryloyloxyethyl lipoate (AOELp), was synthesized and its polymerization behavior was studied. Under conventional radical polymerization conditions, gels were formed due to the competitive independent radical addition to the vinyl groups, affording carbon-centered radicals, and radical ring-opening of the 1,2-dithiolane ring, yielding sulfur-centered radicals, and the ability of both radicals to react with each of the mentioned

polymerizable groups. Prior to gelation, i.e., up to moderate (typically ca. 20 %) monomer conversion, soluble highly branched polymers were formed, which contained a certain fraction of backbone linear disulfide bonds (formed by at least two consecutive cyclic disulfide radical ring-opening reactions or by the radical coupling of two sulfur-centered radicals), and which were partially degradable when treated with reducing agents. On the other hand, the reduction of AOELp (with NaBH<sub>4</sub> or Zn/HCl) lead to the formation of a compound containing two thiol groups and a vinyl group, which, when reacted with bases or with radical initiators, acted as an AB<sub>2</sub>-type monomer in thiol-ene addition reactions. The base-catalyzed or radical thiol-ene self-coupling of the reduced AOELp afforded different highly branched polymers, in which the backbone sulfur atoms were exclusively thioether-type, and which were stable with respect to reduction. This study demonstrates that the same compound is a useful precursor of either degradable or non-degradable highly branched polymers, depending on whether it is reacted with radical sources alone or with radical sources combined with reducing agents (or, as an alternative, only basic reducing agents).

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