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A New Living Emulsion Polymerization Mechanism: Episulfide Anionic Polymerization

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ABSTRACT: The anionic ring-opening polymerization of episulfides has been successfully applied in emulsion. The polymerization proceeded with a living mechanism but was characterized by a limiting conversion, presumably arising from the increase in viscosity in the polymer. To the knowledge of the authors, only two other cases of living anionic polymerization in emulsion are known (silicones and cyanoacrylates); the additional novelty presented by episulifdes is the ease of end-functionalization. Furthermore, the emulsion polymerization allowed the preparation of highly stable particles, which, due to their PEGylated surface and their appropriate diameter, can be applied in the biomedical field as nanocarriers.

Introduction

The application of living polymerization techniques to emulsion processes has been the object of a number of recent papers. Because of the high industrial significance of emulsion radical polymerization, most contributions were devoted to the use of controlled/living radical mechanisms, e.g., nitroxide-mediated polymerization,[1] ATRP,[2] RAFT.[3−6]

Anionic polymerization, probably the most classic example of living mechanism, has on the contrary shown poor compatibility with emulsion processes, due to the high sensitivity to water of the propagating species; only a few cases of anionic emulsion polymerization are reported in the recent literature: the ring-opening polymerization of cyclosiloxanes[7−9] or of epoxides (to our knowledge limited to phenyl glycidyl ether)[10] and the polymerization of cyanoacrylates.[11,12]

Particularly interesting is the last case: the living emulsion polymerization has been coupled to a precise control of the surface composition of the polymer particles, by the use of poly(ethylene glycol) (PEG) as initiator and at the same time emulsifier.[12,13] These particles, due to the PEGylated, protein-repellant surface, are finding applications as nanocarriers for drug-controlled delivery applications.

In the present study we have focused our attention onto a different class of monomers, the episulfides, which are structurally analogous to epoxides and, like them, can be polymerized via anionic ring-opening polymerization; several papers have in detail investigated its mechanism and the physical properties of the resulting polysulfides.[14−25] More recently, propylene sulfide polymerization has shown applicability in the synthesis of amphiphilic block copolymers, where the reactivity of the thiolate-terminated polysulfide chains was used for chain termination or chain extension reactions based on nucleophilic substitution, disulfide formation, and Michael-type addition reactions.[26] The hydrophobic character of monomers and polymers and the mild character of the propagating species (thiolates, good nucleophiles but weak bases, are not sensitive to the presence of most protic groups) suggested to us the possibility to polymerize episulfides also in oil-in-water emulsions; in the present paper we for the first time report the success and the proof of living character for this polymerization.

The episulfide emulsion polymerization could be applied to the water-borne synthesis of well-defined multiblock copolymers; however, having in mind the example of poly(cyanoacrylates), we have targeted the preparation of polysulfide-based nanoparticles. A polysulfide/PEG core−shell structure could be very conveniently used in drug encapsulation: because of the amorphous and rubbery character of the core, high amounts of hydrophobic drugs could be solubilized for a delayed release. At the same time, the well-known polysulfide oxidazibility could provide a stimulus-responsive release in oxidative environment. Finally, the small diameter characteristic of colloidal materials and the PEGylated surface can be advantageous for escaping the capture respectively from capillary networks and organs of the reticuloendothelial system (RES),[27,28] which efficiently removes foreign bodies from the bloodstream.

In this study propylene sulfide (PS) has been used as a standard monomer, 1,3-propanedithiol (PDT) as a bifunctional initiator, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base for deprotonating the initiating thiol. In a living polymerization the bifunctional initiator offers the possibility to exploit end-capping reactions not only for termination or end-functionalization but also for chain extension: in the first case a monofunc-

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Scheme 1

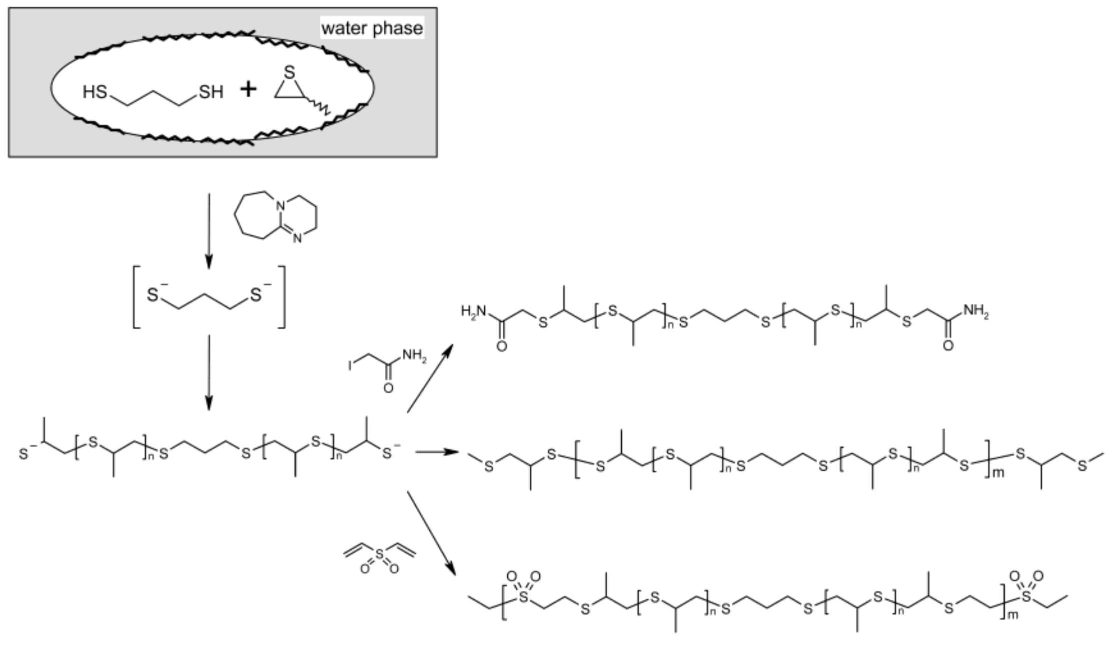

Table 1. Standard Emulsion Polymerization Recipe[a]

monomer/thiol	terminator/initiator	PS (mmol)	PDT (mmol)	DBU (mmol)	terminator (mmol)	Pluronic F-127 (g)
50	1.5	12.76	0.13	0.26	0.38 (IAc)	0.25
50	1.0	12.76	0.13	0.26	0.26 (DVS)	0.25

[a] Abbreviations: PS = propylene sulfide; PDT = 1,3-propanedithiol; DBU = diaza[5.4.0]bicycloundec-7-ene.

tional end-capper, iodoacetamide (IAc), has been used; in the second case, chains have been extended via disulfide bonding or by the use of a bifunctional end-capper, divinyl sulfone (DVS). A survey of the chemical reactions is presented in Scheme 1. Please note that when chain extension is used, the terminal groups of the resulting polymer structure are thiols in the case of disulfide bonding and thiols or vinyl sulfones in the other case (not perfect stoichiometry in the thiolate/DVS ratio determines one or the other termination).

Experimental Part

Solvents and reagents were purchased from Sigma-Aldrich (Buchs, Switzerland) and used without further purification.

^{1}H NMR spectra were recorded on a 300 MHz Bruker spectrometer. FT-IR spectra were recorded in ATR mode on a Spectrum One Perkin-Elmer spectrometer. GPC was performed on 0.1% polymer solutions in THF on a GPC-Viscotek model 300 TDA equipped with triple detection, using a universal calibration with poly(styrene) standards.

The viscosity of emulsions was recorded with a 4° cone and plate CVO 120HR Bohlin rheometer at a shear stress of 5 Pa and at a temperature of 25 °C.

The particle diameter was determined on 0.1% emulsions in double distilled filtered water by static light scattering with a Lexel 95 laser (wavelength of 514 nm at room temperature) and a Brookhaven Instrument model BI-DSI using the BI-9000 particle sizing software.

Emulsion Polymerization. In a typical polymerization experiment, 0.25 g of Pluronic F-127 was dissolved in 25 mL of degassed, double distilled, filtered water in a 100 mL two-neck, round-bottom flask. The system was continuously stirred at 1000 rpm and purged with nitrogen for 20 min before polymerization. Propylene sulfide and 1,3-propanedithiol were then added, and the polymerization was started by adding diaza[5.4.0]bicycloundec-7-ene (DBU) in equimolar quantities with 1,3-propanedithiol. After 2 h an end-capping agent (iodoacetamide) was added in a 1.5 molar ratio with initiating thiols, and the mixture was stirred for 1 h. Compositions used for the polymerization are given in Table 1.

Differently from iodoacetamide, divinyl sulfone was used in equimolar quantities with 1,3-propanedithiol as a chain extender. The presence of vinyl groups at the end of the polymer chains, due to possible slight excess of DVS, was not detected; however, their concentration can be easily below the detection limit of ^{1}H NMR or IR.

Pluronic F-68 and monomethoxy poly(ethylene glycol) 750 were also employed as alternative surfactants in the same amounts as Pluronic F-127.

^{1}H NMR ($CDCl_3$): $\delta = 1.35-1.45$ (d, C$\mathbf{H_3}$ in PPS chain), 1.85−1.95 (q, 2H, in $-S-CH_2-C\mathbf{H_2}-CH_2-S-$), 2.55−2.65 (m, 1 diastereotopic H of C$\mathbf{H_2}$ in PPS chain[29]), 2.85−3.0 (m, C**H** and 1 diastereotopic H of C$\mathbf{H_2}$ in PPS chain[29]), 2.65−2.75 (m, 4H, in $S-CH_2-CH_2-S$ in ethylene sulfide), 3.15−3.25 (d, 2H, $-C\mathbf{H_2}-CONH_2$ in IAc), 3.25−3.35 ppm (q, 2H, $-C\mathbf{H_2}-SO_2-$ in divinyl sulfone).

In most samples, Pluronic was still present after extraction with methanol; the Pluronic quantity was calculated on the basis of its NMR signals compared to those of PPS: 1.05−1.15 (q, CH_3 in PPG segment), 3.6 ppm (s, CH_2 of both PPG and PEG segments).

FT-IR (thin film): 2958 (ν_{as} CH_3), 2865 (ν_s CH_3), 2920 (ν_{as} CH_2), *1683* (ν C=O, amide I band), **1343** (ν_{as} SO_2), 1108 (ν_{as} C−O−C in Pluronic), 800−600 cm^{-1} (ν C−S in PPS). (The characteristic absorption of the iodoacetamide capping are italic, while the one of divinyl sulfone capping are in bold.)

Polymerization of Cyclohexene Sulfide and Copolymerization of Ethylene and Propylene Sulfide. Polymerization with cyclohexene sulfide was performed as described before for propylene sulfide, with a 1:50 molar ratio between initiating thiols and monomer (1:100 molar ratio between 1,3-propanedithiol and monomer). Ethylene sulfide was polymerized in 1:1 molar mixture with propylene sulfide to achieve a statistical copolymerization or by starting the propylene sulfide polymerization and adding an equimolar amount of ethylene sulfide after 1 h. In both cases a 1:50 molar ratio between initiating thiols and total monomers was used.

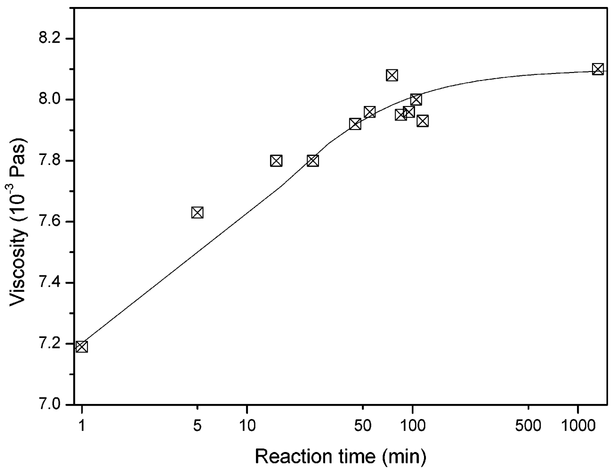

Figure 1. Viscosity of the emulsion as a function of polymerization time. A plateau is reached shortly after 100 s (time axis in logarithmic scale).

All polymers were then end-capped with iodoacetamide after a total polymerization time of 2 h.

Extraction Process. The recovery yields were calculated as weight of recovered polymer/weight of monomer in the feed; two conditions were adopted for extracting the polysulfides from the reaction environment:

Extraction under Mild Conditions: The emulsions were saturated with NaCl and then extracted with two 50 mL portions of dichloromethane. The organic phases were combined and dried over sodium sulfate. After evaporation of the solvent, the viscous material was washed twice with two 25 mL portions of methanol to extract emulsifier and residual monomer. A recovery yield of 20−30% (calculated) was routinely obtained.

Extraction under Drastic Conditions: The emulsions were boiled for 10 min after the addition of 1 mL of acetic acid and then saturated with NaCl; extraction and precipitation were as described above. In nonreducing conditions, the emulsions were exposed to air for 1 h, then boiled for 10 min without the addition of any acid, and then processed as before. Recovery yields ranged between 30% (non-chain-extended polymers) and 60−80% (chain-extended polymers); in the latter case, the analysis of water and methanol phases revealed the absence of any polysulfide product (presence of Pluronic and residual monomer), and thus the recovery was assumed quantitative.

In the first case the dimerization of thiols to disulfides was avoided thanks to the acid treatment: thiolates are the active species in disulfide formation; upon protonation of the thiolates end groups, the polymer chains are more stable against di- or multimerization: exposure of the SH-terminated polymers to air did not produce significant disulfide formation after several hours.

Results and Discussion

Living Character. Episulfide anionic polymerization is known to proceed with a living mechanism, recently exploited also in the synthesis of block copolymers.[26] In that report, the living character was confirmed by the incorporation of a monofunctional end-capper, iodoacetamide (IAc), in 1:1 ratio with the initiating thiols, when used in stoichiometric excess. When in defect, the end-capper was incorporated quantitatively, while exposure to air readily caused dimerization of the non-end-capped, thiolate-terminated polysulfide chains.

The same test was now performed for emulsion polymerization.

After roughly 2 h of reaction the emulsion viscosity reached a plateau (Figure 1).

Interpreting this as a sign of the end of polymerization, the IAc was added in increasing amounts, and its incorporation linearly increased until the 1:1 stoichiometric ratio with the initiating thiols and then reached a plateau (Figure 2). Under reducing conditions (no disulfides; see Experimental Part, extraction process, drastic conditions), the MW remained constant for all the samples (Figure 3); this finding ensured that the end-capping did not promote any parasite reaction. When the samples were exposed to air, they showed a MW increase inversely proportional to the IAc quantity, due to the oxidative disulfide bonding of the non-end-capped chains; the absence of dimerization and therefore of free thiols at and beyond the 1:1 IAc/thiol ratio ensured the quantitative yield of the end-capping and confirmed the living character of the polymerization.

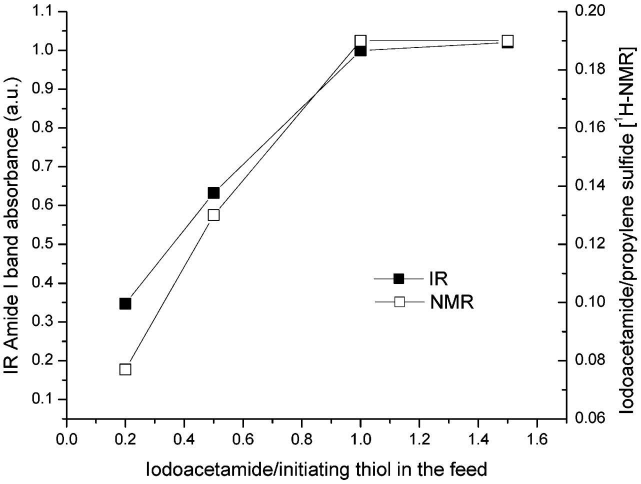

Figure 2. Acetamide incorporation in the polymer as a function of iodoacetamide/initiating thiol ratio. IR data were obtained from the amide I absorption (1683 cm^{-1}), after normalization of the spectra for the aliphatic content (νCH$_2$, 2920 cm^{-1}). ^{1}H NMR data from the ratio between protons in α to the amide group (3.15−3.25 ppm) and methyl protons of the polymer chain (1.35−1.45 ppm); 1:50 initiating thiol: monomer ratio, monomer conversion 27−30%.

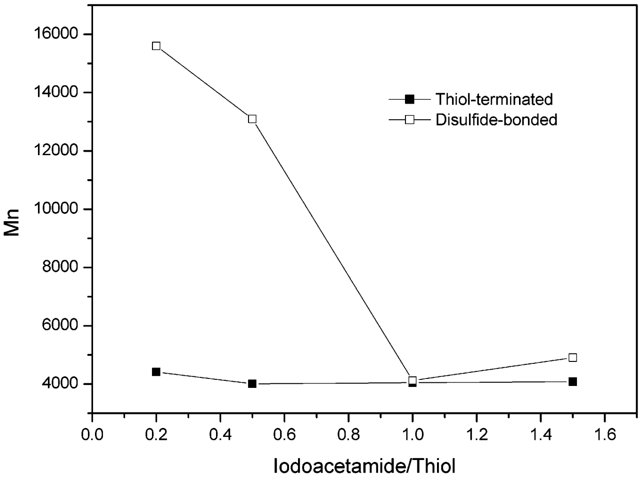

Figure 3. Comparison of $\overline{M}_n$ values (determined by GPC) for polymers isolated in free-thiol form ($\overline{M}_n \propto$ PS degree of polymerization) and after disulfide multimerization ($\overline{M}_n \propto$ PS degree of polymerization × number of disulfides), as a function of iodoacetamide/thiol molar ratio.

Recovery Yields and Reaction Kinetics. For all the samples mentioned above, the $\overline{M}_n$ values (from ^{1}H NMR and GPC) were found to be markedly lower than what expected from the feed (Table 2), a phenomenon difficult to explain for a living polymerization.

Table 2. Characterization Data of Samples End-Capped with Different End-Iodoacetamide/Thiol Ratios; Monomer/Thiol = 50

end-capper/initiator ratio	0.2	0.5	1.0	1.5
monomer/end-capper ratio[a]	130	76	53	55
no. av deg of polymerization[b]	60	54	55	55
mol wt polydispersity[b]	1.15	1.11	1.15	1.15
particle size (nm) (±SD)[c]	130 ± 1.2	134 ± 0.9	159 ± 1.5	153 ± 0.9
size polydispersity[c]	0.22	0.21	0.24	0.23
recovery yield[d]	32	25	32	25

[a] From ^{1}H NMR measurements; ratio between peaks at 1.4 (PPS methyl groups) and 3.2 ppm (IAc protons). [b] From GPC measurements on thiol-terminated samples (see Experimental Part, extraction process); theoretical value (from feed) = 100. [c] From light scattering measurements. The standard deviation (SD) refers to the location of the peak in different samples, while a measurement of the width of the size distribution is given by the size polydispersity. [d] Weight of recovered PPS/weight of monomer. The weight of recovered PPS was calculated measuring the amount of residual Pluronic in the recovered material from ^{1}H NMR and subtracting the corresponding mass.

Three explanations can be considered: (a) isolation of not representative samples after the polymerization, due to low recovery yields (for example, low MW polymers could be preferentially recovered after destabilization of the emulsion), (b) end-capping at incomplete polymerization, and (c) monomer conversion limited by some other factors, such as the increase of viscosity (gel point?) in the organic phase. The occurrence of termination reactions, such as disulfide bond formation, in absence of the aforementioned points is excluded, as shown by the stoichiometric IAc end-capping.

The first point was excluded comparing isolation procedures with different efficiency: the first attempts of polymer recovery were accomplished by salting out the emulsion, extracting the organic matter with dichloromethane, and then washing the polymer with methanol to remove nonadsorbed emulsifier. The low yields of this method (20−30%) were in a second time only slightly enhanced by the addition of water-soluble acids and prolonged boiling: the successful destabilization of the polymer particles was compensated by the loss of most material in the methanol extraction (see Experimental Part).

This last problem was solved by using a bifunctional end-capper (divinyl sulfone (DVS)), acting thus also as a chain extender. This treatment allowed a quantitative recovery of the polymeric material, less soluble in methanol because of the higher MW, but on the other hand left unchanged the degree of polymerization of PS, as calculated from the ratio of initiator and PS peaks in ^{1}H NMR spectra. Additionally, if the ratio between DVS and initiator peaks differs from one, the occurrence of termination reactions could be diagnosed.

The addition of DVS at different times allowed the determination of the degree of polymerization as a function of time (ratio between chain protons and initiator protons), without compromises in the isolation procedure (high MW also with low degree of polymerization).

However, the degrees of polymerization recorded with DVS end-capping were substantially analogous to those obtained with IAc, that is, 55−60% of what calculated from the monomer/initiator ratio (Table 3); the isolation of a nonrepresentative sample (point a) was therefore excluded.

Finally, the end-capper addition at incomplete polymerization (point b) was excluded, too. The quantity of recovered polymer and its degree of polymerization showed a parallel time evolution (Figure 4), as typical for a living polymerization; they reached a plateau after roughly 2 h of polymerization, supporting the viscosity data (Figure 1) in the assumption the polymerization to be stopped when the end-cappers are added.

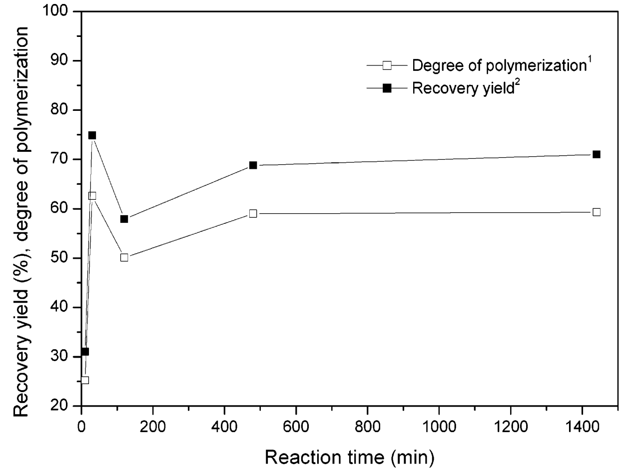

Figure 4. Comparison between recovery yield and degree of propylene sulfide polymerization, calculated as the ratio between monomeric units and initiating units from ^{1}H NMR data (theoretical value = 100).

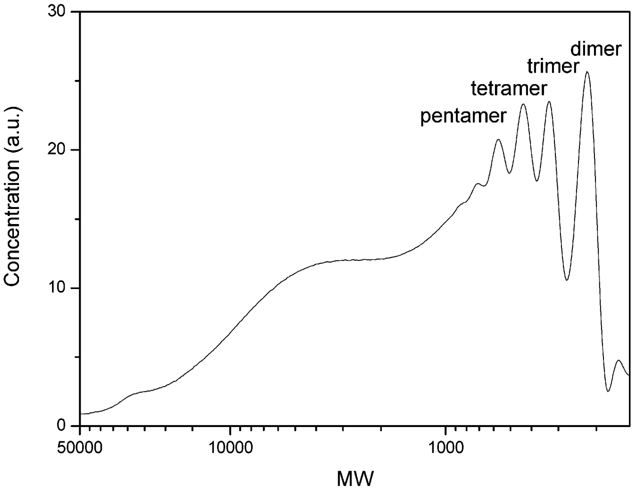

Figure 5. GPC trace for the poly(cyclohexene sulfide) obtained in anionic emulsion polymerization. Eluent: THF, signal: refractive index detector; poly(styrene) calibration.

We therefore concluded that the PS emulsion polymerization, even if perfectly living (no dormant species: the thiolates are still present and reactive), was characterized by a limited monomer conversion (point c); this phenomenon could be due to an increase in the viscosity of the organic phase that dramatically slows down the propagation reaction. However, other phenomena cannot be excluded, such as the partial solubilization of the propylene sulfide in the water phase, with consequent reduction of the monomer available for polymerization.

Polymerization of Other Monomers. The applicability of the emulsion polymerization on other monomers was studied with cyclohexene and ethylene sulfide (ES): The polymerization of cyclohexene sulfide did not lead to well-defined polymers, but to a mixture of oligomers (Figure 5) as it correspondingly happens for the anionic polymerization of the structurally analo-

Table 3. Characterization Data of Samples End-Capped with Divinyl Sulfone as a Function of the Polymerization Time

time of reaction (min)	10	30	120	480	1440
no. av deg of polymerization[a,b]	25.2	62.6	50.1	59.0	59.3
particle size (nm) (±SD)[c]	139 ± 2.0	137 ± 4.0	113 ± 1.1	124 ± 0.9	119 ± 1.2
size polydispersity[c]	0.29	0.28	0.23	0.13	0.15
recovery yield[d]	31	75	58	69	71

[a] From ^{1}H NMR measurements; from the ratio between peaks at 1.4 (PPS methyl groups) and 1.9 (initiator protons) ppm; theoretical value (from feed) = 100. [b] The absolute molecular weight of the chain-extended polymers is not inherent to the emulsion polymerization mechanism and shows high dispersion and variability (the yield of the Michael-type reaction depends also on the viscosity of the organic phase); thus, it is not reported in this paper. [c] From light scattering measurements after divinyl sulfone addition. The standard deviation (SD) refers to the location of the peak in different samples, while a measurement of the width of the size distribution is given by the size polydispersity. [d] Weight of recovered PPS/weight of monomer. The weight of recovered PPS was calculated measuring the amount of residual Pluronic in the recovered material from ^{1}H NMR and subtracting the corresponding mass.

Table 4. Characterization of Propylene and Ethylene Sulfide Copolymerization Products

	statistical copolymerization	block copolymerization
no. av deg of polymerization[a]	22.0	62.2
ethylene sulfide/propylene sulfide[c]	1.2	1.0
particle size (nm) and dispersity (±SD)[d]	178 ± 3.0	114 ± 1.1
size polydispersity[d]	0.28	0.23
recovery yield[e]	18	49

[a] From ^{1}H NMR measurements; ratio between peaks at 1.4 (PPS methyl groups) and 1.9 (initiator protons) ppm. [b] From ^{1}H NMR measurements; ratio between peaks at 1.4 (PPS methyl groups) and 3.2 (IAc protons) ppm. [c] From ^{1}H NMR measurements; ratio between peaks at 2.6 (ES CH_2 groups) and 1.4 (PPS methyl groups) ppm. [d] From light scattering measurements. [e] Weight of recovered PPS/weight of monomer. The weight of recovered PPS was calculated from the weight of the total recovered material, subtracting the amount of coprecipitated Pluronic; the latter value was calculated from the PPS/Pluronic ratio as seen in ^{1}H NMR spectra.

gous cyclohexene oxide (generally polymerized via cationic photoinitiated polymerization[30]).

Poly(ethylene sulfide) is a highly crystalline and insoluble polymer, which often precipitates from the polymerization environment; for a better characterization of the product, it was therefore copolymerized with propylene sulfide to produce statistical or block copolymers (by late addition of ethylene sulfide) with enhanced solubility. Starting from a 1:1 ES/PS ratio in the feed, the random and the blocky copolymers presented a 1.2:1 and a 1:1 ES/PS ratio, respectively (based on ^{1}H NMR analysis). A particularly low monomer conversion and correspondingly a low degree of polymerization were recorded for the statistical polymerization, suggesting ethylene sulfide to be incorporated faster in the polymer chain and probably stopping faster the polymerization reaction, likely by increase of viscosity or crystallization. On the other hand, the 1:1 monomer ratio and the higher conversion in the block copolymer showed the poly(propylene sulfide) chain to be still active for polymerization and not only for end-capping and the blocky structure to be more active than the random one in monomer incorporation (Table 4).

Polymerization with Other Surfactants. Substituting Pluronic F-127 (MW ~ 12 000, 70% PEG) with the more hydrophilic Pluronic F-68 (MW ~ 9000, 80% PEG) the polymer particles doubled in size (286 vs 110 nm), possibly indicating agglomeration. The even more hydrophilic monomethoxy poly(ethylene glycol) (MW = 750) was not able to stabilize the particles at all, and coalescence was observed during the reaction.

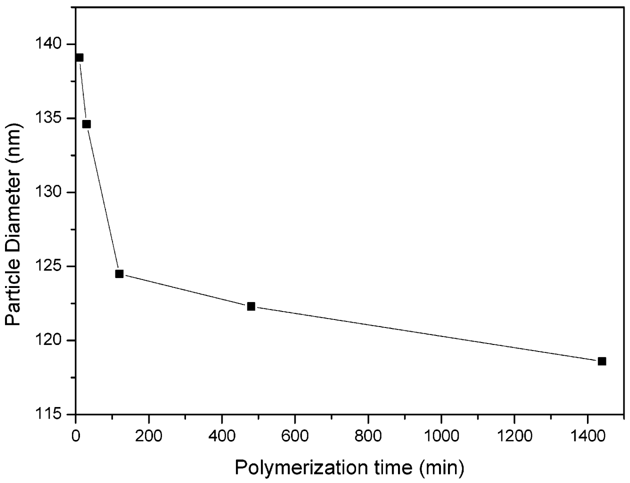

Figure 6. Particle diameter as a function of polymerization time. Light scattering data recorded after divinyl sulfone end-capping.

Table 5. Influence of Stirring Speed on Particle Diameter

stirring speed (rpm)	300	600	1000
particle size (nm) and dispersity (±SD)[a]	143	122	153
size polydispersity[a]	0.29	0.28	0.23

[a] From light scattering measurements.

Particle Diameter. The average particle diameter was measured as a function of polymerization time after quenching the reaction with DVS. A decrease from roughly 140 to 110 nm was observed. We assume the end-capping reaction not to affect the particle dimensions and thus the shrinkage to depend mainly on the monomer conversion. This assumption is supported by the fact that the change in dimensions has a similar, but opposed, time behavior to the degree of polymerization and recovery yield (Figure 6).

The stirring speed (varied between 300 and 1000 rpm) did not markedly influence the particle size obtained after a polymerization of 2 h (Table 5).

Polymerization Locus. The following considerations let us suppose the polymerization to take place in the monomer droplets: the active species (monomer, initiator; the base just activates the initiator) are contemporarily present in the oil phase; the particle size is reduced when conversion increases (shrinking due to polymerization). Under the limiting conversion hypothesis, if the process is initiated out of the monomer droplets, high-viscosity particles would be produced already in the early stages of polymerization, thus stopping it at the level of oligomers. On the contrary, the viscosity greatly increases only after a strong monomer consumption.

Conclusions

Episulfides can be polymerized in emulsion in a living fashion. The polymerization has been studied in detail for propylene sulfide and showed applicability also to its copolymers with ethylene sulfide.

The analysis of emulsion viscosity, of particle size, and of degree of polymerization showed the polymerization to stop after roughly 2 h. On the contrary, the end-group reactivity was retained; termination by oxidative disulfide coupling readily occurred only by exposure to air. This finding lead us to suppose the polymerization to be characterized by a limiting conversion, maybe due to the viscosity increase inside of the particles: (a) it is a material property and not a chemical change to determine the limited conversion (dormant state of the material, no dormant species), (b) the viscosity is the property that shows the most drastic and nonlinear change during polymerization, thus the most likely to cause a strong decrease in the propagation rate, and (c) the block copolymerization can be easily explained by the fact that the addition of a second monomer also determines a drop in the viscosity, so that the propagation can take off again.

The particles obtained via PS emulsion anionic polymerization showed a straightforward stability toward agglomeration; extraction with organic solvents and salting out of the water phase did not significantly cause particle agglomeration, which was on the contrary obtained only after prolonged boiling. This stability is presumably to ascribe to the strength of Pluronic surface adsorption on the hydrophobic particles, as already seen e.g. for poly(styrene)[31] and poly(lactic acid).[32]

Characteristics such as the high stability, the submicron size, and the PEGylated surface make these particles attractive for applications as carriers in biomedical applications and more specifically for the delivery of hydrophobic drugs, such as most steroidal hormones. Because of the mild character of the propagating species (the thiolates), many sensitive compounds could be dispersed already in the monomer mixture, eliminating the necessity of a successive loading stage. The living polymerization mechanism gives an additional advantage in the possibility to covalently link functional groups at the end of the polymer chain, while bioactive and directing groups can be attached at the ends of the surface-immobilized Pluronic macromolecules.

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