Microgel Preparation by Miniemulsion Polymerization of Passerini Multicomponent Reaction Derived Acrylate Monomers

*Julian Tobias Windbiel, Audrey Llevot,**

Julian Windbiel

Karlsruhe Institute of Technology (KIT), Laboratory of Applied Chemistry, Institute of Biological and Chemical Systems – Functional Molecular Systems (IBCS-FMS), Eggenstein-Leopoldshafen, 76344, Germany.

Dr. Audrey Llevot

Bordeaux INP, University of Bordeaux, Laboratoire de Chimie des Polymères Organiques, UMR 5629, ENSCBP, 16 avenue Pey-Berland, F-33607, Pessac cedex, France.

E-mail: audrey.llevot@enscbp.fr

Keywords: microgels, nanoparticles, miniemulsions, multicomponent reactions, Passerini reactions

Abstract

Three acrylate monomers featuring different side-groups are synthesized in yields up to 94 % in a one-pot procedure using the versatile Passerini-three-component reaction. The procedure for their miniemulsion polymerization into polymeric particles with tunable sizes is established. Ethylene glycol dimethacrylate is introduced as comonomer to induce crosslinking and enable the production of microgels. Besides the shelf life of the miniemulsions, the dependence of the particle size on the concentration of the surfactant (sodium dodecyl sulfate) and the crosslinker, as well as the sonication amplitude and time, is investigated. The particle size of the collapsed microgels range from 21 nm to 91 nm. The swelling of the microgels in organic solvents is studied.

1. Introduction

Nowadays, microgels find applications in a multitude of area such as the fabrication of organic coatings,[1] drug delivery,[2] cell imaging,[3] tissue engineering,[3] catalysis,[4] or optical sensors or switches.[5] Microgels are crosslinked polymeric colloidal particles with submicrometer or micrometer sizes that exhibit internal gel-like structures.[6–9] These colloidal polymer networks feature the ability to swell in solvents and be loaded with various substrates.[10–11] Swelling/deswelling can be triggered by temperature,[12,13] pH of the solvent,[14] and the solvent itself. This property is adjustable depending on the chemical and topological structure of the microgels.

The research field is largely dominated by aqueous microgels, such as poly(*N*-isopropylacrylamide) microgels,[15] which are thermoresponsive.[5] Although examples of non-aqueous microgels that show swelling in organic solvents are scarce, they are of industrial and academic relevance, for instance for applications as photonic crystals,[16]

molecular imprinting systems,[17] or as binders in organic coating.[18] The synthesis of microgels can be performed in homogeneous (solution polymerization) or heterogeneous phase (precipitation or dispersion polymerization).[8] Among the heterogeneous techniques, miniemulsion polymerization constitutes a versatile tool.[19]

Miniemulsions consist of a system of two immiscible liquids, one being dispersed in the other using a high shear device.[20] Typically, oil droplets with diameters between 50 nm and 500 nm are stabilized in an aqueous medium (direct miniemulsion).[21] The stability of the system against coalescence and Ostwald ripening is usually reached by the introduction of an ionic, water-soluble surfactant and a hydrophobic cosurfactant, respectively.[20,22,23] Landfester *et al.* showed that the particle size mainly depends on the amount and type of surfactant.[21,23] Higher surfactant concentrations typically lead to smaller particles.[21,23] Miniemulsions are compatible with most polymerization mechanisms and, in the presence of a crosslinker, yield microgels with tunable particle size and narrow size distributions. A wide variety of vinylic monomers were polymerized in miniemulsion, ranging from apolar monomers such as vinyl chloride or styrene through vinyl acetate and methacrylate[20] to water-soluble monomers like acrylamide,[24] acrylic acid[25] or *N*-isopropylacrylamide [26] that are polymerizable in inverse miniemulsions. The monomer structure influences the microgel swelling behavior and thus, many properties such as loading capacity and rheological properties. Therefore, the development of novel monomers for microgel synthesis is central for a broad range of applications.

Multicomponent reactions (MCR) are valuable tools to quickly access monomer/polymer libraries due to their modular character. Since their introduction to polymer science in 2011, MCRs have been widely used for monomer synthesis, as polymerization and post-polymerization modification techniques, as well as for architecture control, sequence control

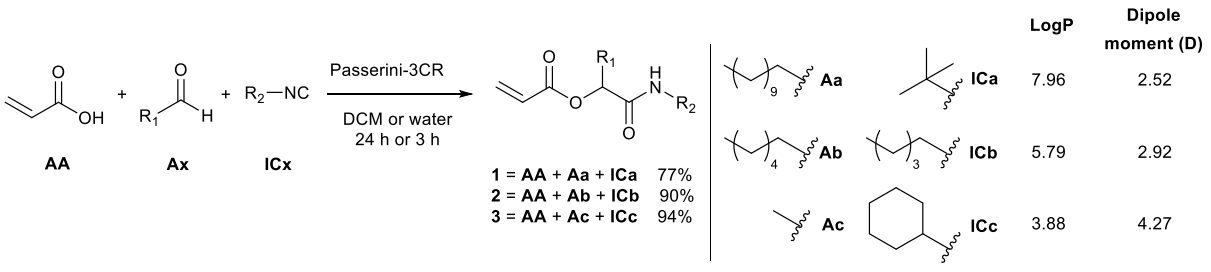
and sequence definition.[27-34] MCRs are one-pot procedures with high atom economy and yields that are considered as resource and time-efficient.[35] As the molecular diversity of the samples is easily reached through different combinations of reactants, series of vinylic monomers have been synthesized by different groups.[36–42] Especially the Passerini three-component reaction (P-3CR) using (meth)acrylic acid provided (meth)acrylate monomers in a versatile fashion. The P-3CR was discovered in 1921 by Mario Passerini and involves the reaction of a carboxylic acid, a ketone or aldehyde, and an isocyanide to form α-acyloxycarboxamides.[43,44] While bulk polymerization of vinylic monomers synthesized *via* P-3CR remains the majority, Roth and Lowe used Reversible Additon Fragmentation Chain-Transfer dispersion polymerization to prepare reactive nanoparticles from thiol-reactive Passerini-derived monomers.[45] This polymerization induced self-assembly produced several morphologies depending on the degree of polymerization, including pure spherical nanoparticles for the lowest degree of polymerization.[46]

Herein, we report the oil in water miniemulsion polymerization of three acrylate monomers synthesized *via* P-3CR of acrylic acid with different aldehydes and isocyanides. First, the miniemulsion polymerization of the P-3CR derived acrylate monomers was investigated in the absence of crosslinker. The influence of several parameters such as the amount of surfactant and ultrasound amplitude and time on the particle size and miniemulsion stability was studied. Then, ethylene glycol dimethacrylate (EGDMA) was added to the optimized miniemulsion procedure to yield crosslinked microgels. The resulting gels, as well as their swelling properties, were characterized.

2. Results and Discussion

2.1 Monomer Synthesis *via* Passerini-3CR

The synthesis of acrylate monomers *via* a multicomponent reaction enables the straightforward incorporation of different functional groups into a monomer and polymers thereof. Two new and one known acrylate monomers with side chains were synthesized *via* Passerini-3CR similarly to literature (**Scheme 1**).[36] Syntheses were performed using 1 eq of acrylic acid (AA) and 1.5 eq of the respective aldehyde (Ax) in water or dichloromethane, depending on the water solubility of the product. After the dropwise addition of 1.5 eq of the respective isocyanide (ICx) the mixture was stirred for one day (dichloromethane), or 3 h (water). While acrylate 1 was isolated with a yield of 77%, the acrylate 2 and 3, which were synthesized in dichloromethane, were obtained in yields over 90%. The difference can be attributed to the purification methods. Although the purification of 2 and 3 was performed *via* column chromatography, the separation of acrylate 1 from the excess lauric aldehyde was not complete using this method. Thus, pure acrylate 1 was obtained by recrystallization from *n*-hexane. The yield was affected by the partial solubility of 1 in this solvent. The purity was confirmed by GC-MS and NMR (for spectra and chromatograms see **Figure S1 – S4**). The monomers were stored in the fridge at 4 °C.



Scheme 1 Monomer synthesis by Passerini-3CR, LogP and dipole moment values calculated by DFT.

Density Functional Theory (DFT) was used to compare the hydrophobicity and polarity of the three monomers. The values of LogP, which is the octanol/water partition coefficient, decrease from monomer 1 to monomer 3, from 7.96 to 3.88. In contrast, the values of the dipole moments

of these monomers increase from monomer 1 to monomer 3, from 2.52 D to 4.27 D. These results are directly linked to the chemical structure of the monomer side chains (R_1 and R_2). Monomers with longer alkyl chains are more hydrophobic and less polar. The combination of DFT calculations and Passerini-3CR offers an efficient solution for the design of acrylates with chemical and physical propreties meeting requirement of specific applications.

2.2 Polymerization in Solution

Prior to miniemulsion polymerization, the reactivity of the monomers in Free Radical Polymerization (FRP) was initially tested in solution. Acrylates 1-3 were polymerized in ethyl acetate at 70 °C using azobisisobutyronitrile as initiator. The molecular weigth of the of the crude products was determined by Size Exclusion Chromatography (SEC) in THF (**Table 1**, for chromatograms see **Figure S5**). The solubility of P1 in THF was low, which impeded its accurate characterization. P2 and P3 exhibited molecular weights (M_n) of 38.4 kg mol^{-1} and 101.3 kg mol^{-1}. Since the synthesized monomers were polymerizable by FRP, their miniemulsion polymerization was investigated.

Table 1 SEC data of the crude products after the FRP of acrylates 1-3 in solution.

Monomer	Polymer	M_n [kg mol^{-1}]	M_w [kg mol^{-1}]	$Đ$
1	P1	Low solubility in THF		
2	P2	38.4	116.9	3.04
3	P3	101.3	302.8	2.98

2.3 Miniemulsion Polymerization

To synthesize reproducible and tunable nanoparticles and microgels, a suitable composition and preparation method for miniemulsions, containing the respective components, was set up as follows if not stated otherwise, similarly to Landfester *et al.*[23] Miniemulsions were prepared

using water as continuous phase. The respective monomers (and crosslinker) were dissolved in tertbutyl acetate with 1.9 mol% hexadecane and added to the sodium dodecylsulfate (SDS) containing continuous phase in approximately 2 wt% (organic phase in aqueous phase). After 1 h of pre-emulsification (vigorous stirring) and subsequent sonication for 2 min at an amplitude of 60%, the miniemulsion was obtained. This procedure led to emulsions with a macroscopic shelf life of more than 3 d. For all following investigations, the miniemulsions were directly polymerized by FRP after preparation since the droplets were not stable upon dilution during the sample preparation for dynamic light scattering (DLS). Potassium peroxydisulfate (KPS) was chosen as radical initiator due to its water solubility. The miniemulsions were polymerized by addition of potassium peroxydisulfate, purging with argon, and subsequent stirring at 85 °C for 3 h under argon (**Scheme S1**).

The influence of the sonication time and amplitude, and surfactant concentration, as well as the reproducibility, were investigated using monomer 1 without addition of a crosslinker (**Figure 1**, **Table S1**). In the following paragraphs, the surfactant concentration is given as the weight ratio of surfactant to monomer *S*.

No difference in particle size was observed when sonication was applied for different times (0.5 min, 1.0 min, 2.0 min with $S = 0.010$, amplitude = 60 %) but a slight difference in the size dispersity was visible. The distributions were broader for sonication times lower than 2 min. This result differs from literature where the sonication time, in a range of 0 to 10 min with $S = 0.010$, was shown to influence the particle size of the miniemulsion polymerization of styrene.[23]

A variation of the sonication amplitude (30-100%) led to a small decrease of the particle size (from 51 nm to 38 nm) with an increase of the applied shear forces. The polydispersity index (*PDI*) values were between 1.16 and 1.88 and did not follow a visible trend.

The particle size was successfully controlled in a range from 33 nm to 91 nm by a variation of *S* between 0.002 and 0.100. Higher amounts of surfactant led to smaller particles counteracting the increased surface tension of smaller droplets. To ensure the reproducibility of the method, two experiments were performed under identical conditions (2 min, 60%, $S = 0.010$). The DLS measurements showed similar particle size distributions with diameters of 44 nm and *PDI*s of 0.153 and 0.162.

The successful polymerization was confirmed by SEC (**Table S2**). Polymers exhibited M_n values from 39 to 81 kg mol^{-1} with dispersities of 5.1 to 6.4. respectively.

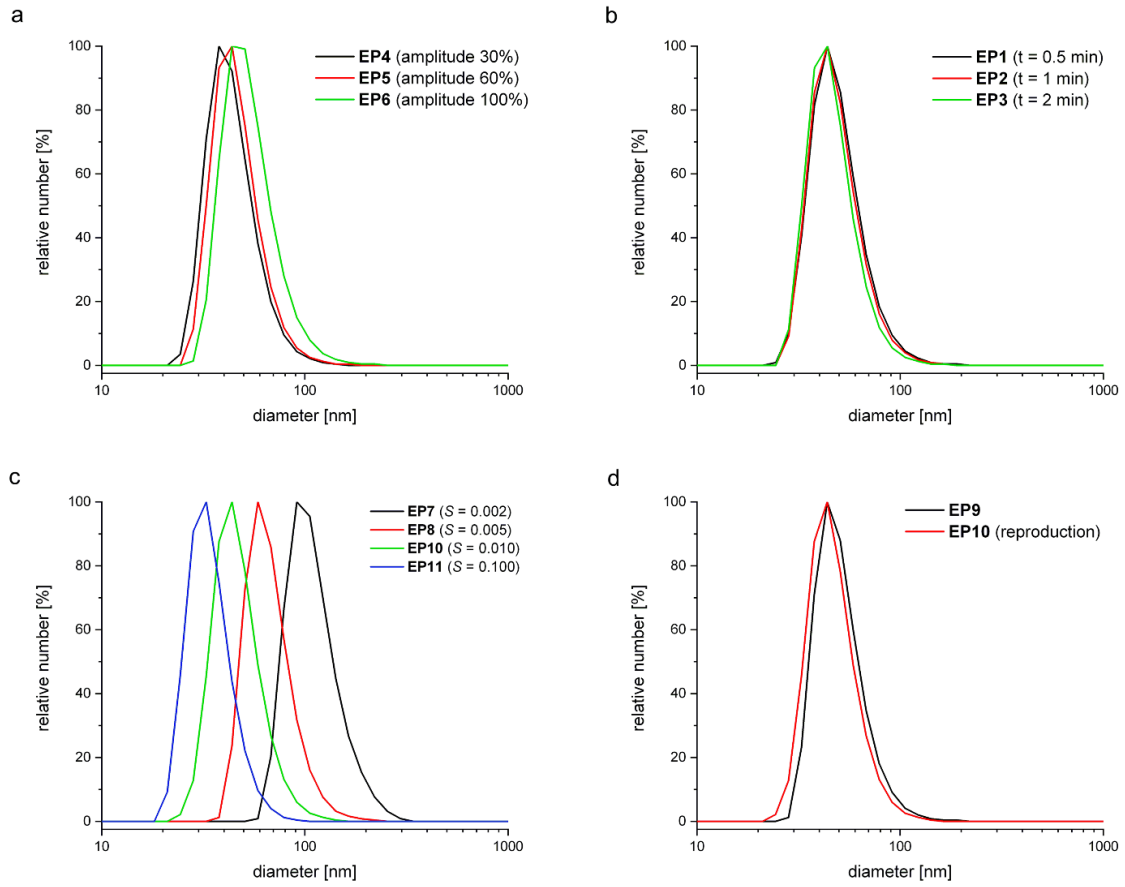


Figure 1 DLS results of non-crosslinked particles synthesized from monomer 1: influence of the sonication amplitude (a), sonication time (b), surfactant concentration (c) on the particle

size; reproducibility (d) (if not stated otherwise S = 0.010, sonication time = 2 min, amplitude = 60%).

2.4 Microgel Synthesis

The microgel synthesis was investigated using the protocol described in the previous section but with addition of the hydrophobic crosslinker ethylene glycol dimethacrylate (EGDMA).

2.4.1 Miniemulsion Stability

Miniemulsions are critically stable systems, *i.e.* the particle size is changing over time. The thermodynamically driven Ostwald ripening, caused by the Laplace pressure, is slowed but not stopped by an osmotic pressure generated by the hydrophobe. Hence, the particle size is increasing over time until a stable colloidal system is reached. The polydispersity is lowered drastically during the equilibration process.[46] To determine the emulsion stability and observe the equilibration process, several identical emulsions of acrylate 1 and EGDMA were prepared and polymerized (by adding of the initiator after determined time) after certain time delays following the above described procedure. While the particles directly after miniemulsification exhibited diameters of around 30 nm and *PDI* of 0.217, the particle size gradually increased and the *PDI* decreased to reach an equilibrium after around one week yielding particles of 110 nm with a *PDI* of 0.061 (**Figure 2**). As after half a day, the particle size is 60 nm, the maturing process is rapid on the timescale of sample preparation. Consequently, the direct polymerization after emulsification is crucial to synthesize reproducible microgels.

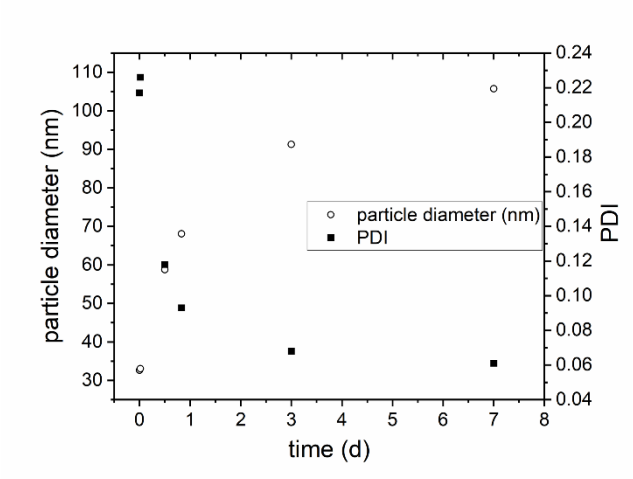


Figure 2 DLS results of the maturing of miniemulsions.

2.4.2 Polymerization

The successful incorporation of the crosslinker into the acrylate polymer was hinted by the insolubility of the dried crude products in tetrahydrofuran contrary to the non-crosslinked nanoparticles. As this insolubility prevented SEC measurements, the conversions of monomer and EGDMA were determined by gas chromatography-mass spectrometry (GC-MS) analyses. Miniemulsion were sampled before introduction of the initiator and after defined reaction times. After removing the water under high vacuum (less than 10^{-2} mbar), the sample was stirred in ethyl acetate for 20 min and filtered to remove the crosslinked nanoparticles. The remaining solution was analyzed by GC-MS. The soluble part contained unreacted monomer and hexadecane which serves as the internal standard. After 3 h reaction time, the conversion of the acrylate monomers 1-3 was above 95% and the conversion of EGDMA was quantitative in each case (for GC-MS chromatograms see **Figure S6 – S8**).

2.4.3 Influence of Surfactant and Crosslinker Concentrations

To confirm the influence of surfactant concentration on the particle size as observed for the non-crosslinked nanoparticles, miniemulsions of 1 with three different SDS concentrations were polymerized and characterized by DLS. The miniemulsion with $S = 0.010$ was prepared twice to verify reproducibility (**Figure 3, Table 2**). The superposition of the two DLS profiles,

with the same calculated particle diameters of 38 nm and *PDIs* of 0.200 and 0.194, shows the reproductibility of the procedure. Increasing the surfactant ratio from 0.005 to 0.100 resulted in a decrease of the particle diameter from 51 nm to 21 nm. (**Figure 3, Table 2**). As a result, the possibility to control the particle size by tuning the surfactant ratio was also shown for the microgel preparation. Noteworthy, the non-crosslinked particles described in section 3.2 exhibit slightly larger particle sizes for the same SDS concentration compared to those of the microgels. This decreased swellability can be attributed to the presence of crosslinking points.

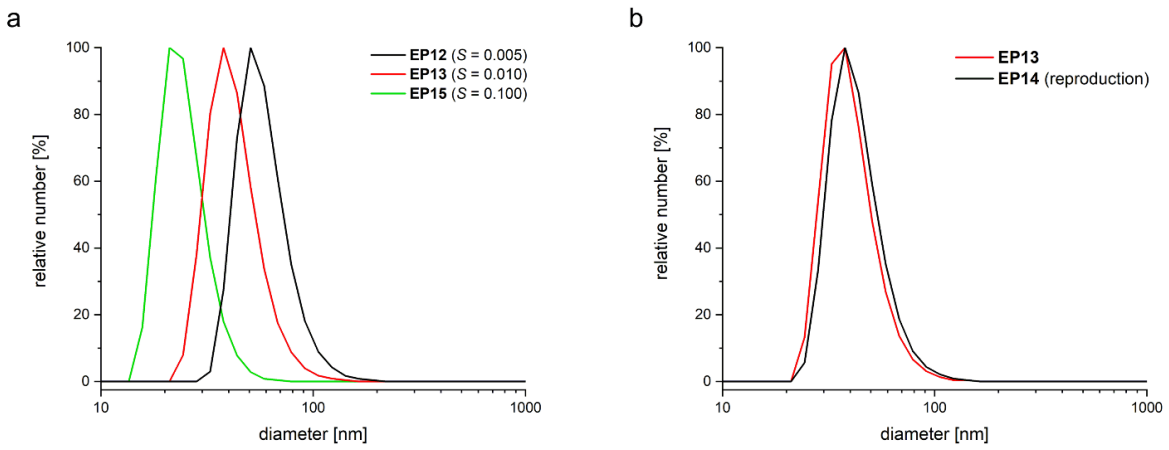


Figure 3 DLS results of the influence of the surfactant concentration on microgels prepared from monomer **1** (a); reproduction (b) (if not stated otherwise S = 0.010, sonication time = 2 min, amplitude = 60%, 10mol% EGDMA).

Table 2 Investigation of the dependency of particle size and PDI of microgels on the surfactant concentration (monomer 1, sonication time = 2 min, amplitude = 60%).

Emulsion polymerization	*S*	*d* [nm]	*PDI*
EP12	0.005	51	0.150
EP13	0.010	38	0.200
EP14[a)]	0.010	38	0.194
EP15	0.100	21	0.134

a) reproduction

Polymerizations of the monomers 1-3 with different amounts of EGDMA (5 mol%, 10 mol%, 15 mol%) (**Figure 4**, **Table 3**) were performed to investigate the influence of the amount of crosslinker on the particle size. A trend is only visible on the microgel synthesized from monomer 2, as it exhibits the largest particle size. Each 5 mol% increase of EGDMA resulted in a size growth of around 15%. This tendency can be attributed to a better solubility of the crosslinker in water compared to the monomer, which would lead to a slight swelling of the final particle size. The small particle size of the microgels prepared from the other monomers might prevent the observation of significant change. Moreover, the DLS analyses of the microgels synthesized from monomer 3 revealed an additional phenomenon. Indeed, the intensity percentage diagram shows that particles with different sizes (two populations) were formed (33 nm and ~142 nm) (**Figure S9**). As the other two monomers did not show this behavior, the second population might be attributed to the higher water solubility of monomer 3, which can result in homogeneous nucleation could occur.

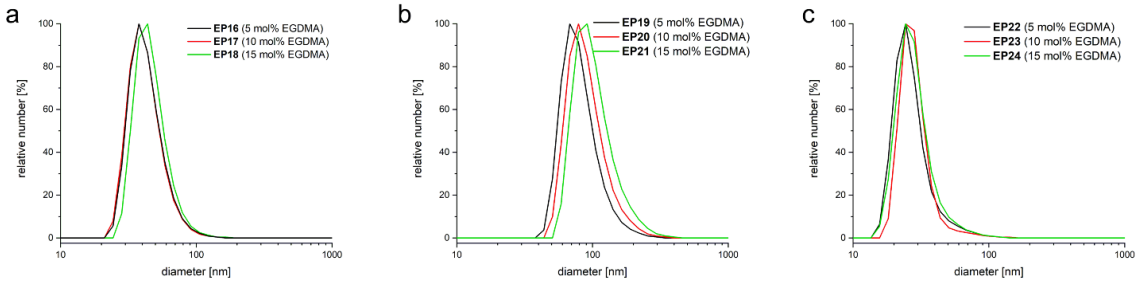


Figure 4 DLS results of the variation of crosslinker concentration with monomer **1** (a), **2** (b), and **3** (c) (S = 0.010, sonication time = 2 min, amplitude = 60%).

Table 3 DLS results of microgels synthesized with different amounts of EGDMA (sonication time = 2 min, amplitude = 60%, S = 0.010).

Emulsion Polymerization	monomer	x_{EGDMA} [mol%]	*d* [nm]	*PDI*
EP16	1	5	38	0.194
EP17	1	10	38	0.200
EP18	1	15	44	0.206
EP19	2	5	68	0.153
EP20	2	10	79	0.127
EP21	2	15	91	0.130
EP22	3	5	24	0.181
EP23	3	10	24	0.200
EP24	3	15	24	0.182

2.4.4 Swelling Behavior

The size of microgels depends on their environment and especially on the nature of the solvent. If the intermolecular interactions between the solvent and polymer chains are favored, the microgel will swell. On the contrary, if the polymer-polymer and solvent-solvent interactions are more favorable, the microgel will collapse. Thus, samples of the freeze-dried microgels were vigorously stirred in different solvents (methanol, ethanol, and tetrahydrofuran) overnight to allow proper redispersion and swelling. The resulting dispersions were analyzed by DLS (**Figure 5**, **Table 4**). Microgel EP17 from monomer 1 showed increased hydrodynamic diameters in the three organic solvents compared to water. The strongest swelling (255 nm) was observed in ethanol. Microgel EP20, synthesized from monomer 2, exhibited the largest diameters in methanol with 190 nm. The diameters in ethanol and tetrahydrofuran were smaller (51 nm and 59 nm, respectively) than in water (79 nm). Microgel EP23, synthesized from

monomer 3, displayed larger diameters in organic solvents compared to water (24 nm). However, the increase in size was approximately two times lower compared to EP17 and EP20.

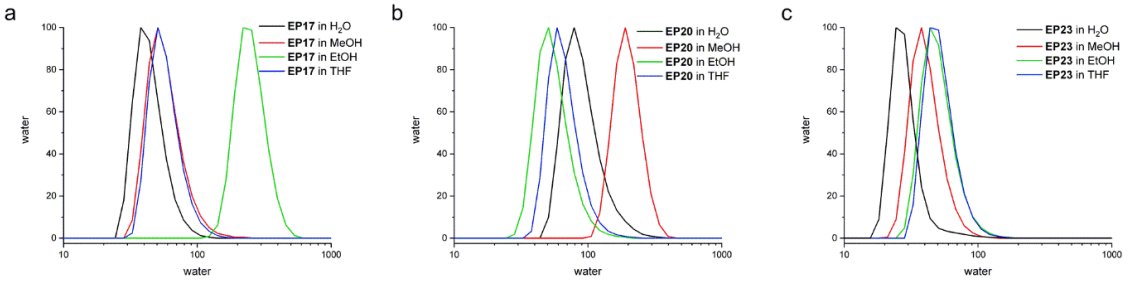


Figure 5 DLS results of the swelling experiments of microgels from **1** (a), **2** (b), and **3** (c) (the measurements in water for **EP20** and **EP23** were done prior to freeze-drying).

Table 4 DLS results of the swelling experiments.

Emulsion Polymerization	Diameter [nm] in different solvents (*PDI*)				*Q*[b]		
	H_2O	MeOH	EtOH	THF	MeOH	EtOH	THF
EP17	38 (0.146)	51 (0.233)	238 (0.403)	51 (0.269)	1.34	6.25	1.34
EP20	79 (0.127)[a]	190 (0.252)	51 (0.207)	59 (0.260)	2.41	0.646	0.747
EP23	24 (0.200)[a]	38 (0.234)	44 (0.354)	51 (0.381)	1.58	1.83	2.13

a) DLS data prior to freeze-drying; b) Particle diameters in organic solvents relative to the particle size in water.

2.4.5 Imaging of the Microgels via AFM

To provide additional evidence of the successful preparation of microgels, the microgel EP17 (synthesized from monomer 1) was imaged *via* Atom Force Microscopy (AFM). The polymerized emulsion was highly diluted in methanol and one drop of the resulting mixture was evaporated on a glass microscopy slide to avoid agglomeration. The obtained image (**Figure 6**) showed the existence of nanoparticles with an average particle size of 279 nm. This diameter was similar to the diameters of 220 – 255 nm, calculated by DLS during the swelling.

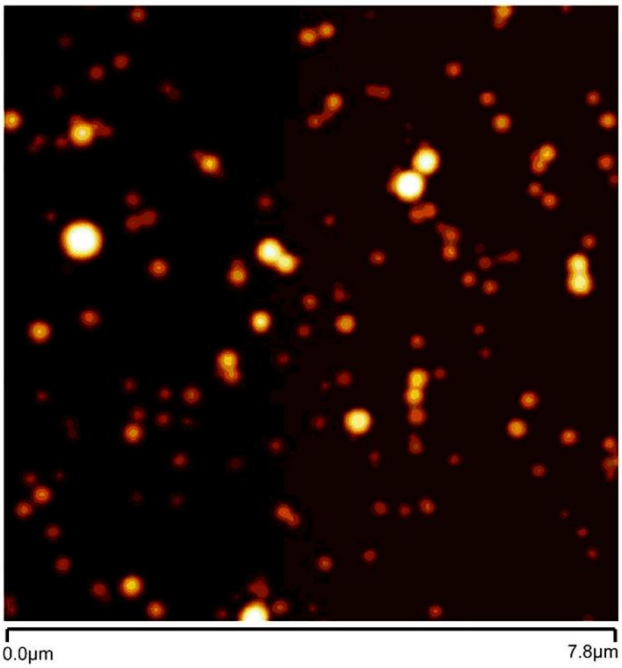


Figure 6 AFM image of **EP17**: Distinct particles are visible. Their average diameter of 278 nm is similar to the diameter determined via DLS. (1.5 column figure)

3. Conclusion

Herein, a procedure for the miniemulsion polymerization of three acrylate monomers of different polarity, prepared by Passerini-3CR, was established to synthesize microgels with tunable particle sizes. The pure acrylate monomers were obtained in yields up to 94%. The miniemulsion polymerization procedure was first optimized in terms of composition and sonification amplitude and time for the acrylate monomers without addition of crosslinker. Reproducibility and the tunability of the particle size *via* variation of the concentration of surfactant was verified. Subsequently, the miniemulsion polymerization procedure was applied for the synthesis of microgels using ethylene glycol dimethacrylate as crosslinker in three different concentrations. Microgels with particle sizes in the range from 21 nm to 91 nm were obtained by a variation of the amount of surfactant and crosslinker. In addition, the behavior of the microgels in methanol, ethanol, and tetrahydrofuran was investigated. This study demonstrated the siutability of acrylate monomers synthesized by Passerini reaction for

miniemulsion polymerization and microgel synthesis. In the future, the modularity of this multicomponent reaction should be exploited for the preparations of libraries of acrylates with different side groups and polarities and the microgels thereof to cover a broader range of swelling behaviors and rheological properties. The methodology described in this work is promising to identify suitable structures of acrylate-based microgels to meet specific requirements of coating technologies or rheology modifiers.

4. Experimental Section

4.1 Materials

Azobisisobutyronitrile (98%), dodecyl aldehyde (95%) acrylic acid (99%), ethylene glycol dimethacrylate (98%), heptyl aldehyde (95%), pentyl isocyanide (97 %), tertbutyl acetate (99%), tertbutyl isocyanide (98%) and potassium peroxydisulfate (99%) were supplied by Sigma Aldrich, cyclohexyl isocyanide (97%) and SDS (98%) by Acros Organics, hexadecane (99%) by Alfa Aesar, acetaldehyde (99%) by Fluca Analytical. Acrylic acid was distilled and stored at 8 °C before usage. The applied solvents, namely acetone, cyclohexane, dichloromethane, diethyl ether, ethanol, ethyl acetate, n-hexane, methanol, and tetrahydrofuran were distilled before usage.

4.2 Monomer Synthesis

4.2.1 1-(tert-butylamino)-1-oxotridecan-2-yl acrylate 1: Freshly distilled acrylic acid (25 mmol, 1 eq) and lauryl aldehyde (37.5 mmol, 1.5 eq) were mixed in 100 mL of deionized water. Under stirring and ice-cooling, tertbutyl isocyanide (37.5 mmol, 1.5 eq) was added dropwise to the solution. The mixture was then vigorously stirred for 3 h at room temperature. The product precipitated during the reaction and was afterward purified by recrystallization from *n*-hexane yielding 77% as white powder.

^{1}H NMR (300 MHz, $CDCl_3$, δ (ppm)): 6.48 (d, J = 17.2 Hz, 1H, H1a), 6.18 (dd, J = 17.2, 10.5 Hz, 1H, H2), 5.92 (d, J = 10.3 Hz, 1H, H1b), 5.80 (br. s, 1H, H10), 5.12 (t, J = 5.6 Hz, 1H, H6), 1.93-1.75 (m, 2H, H7), 1.34 (s, 9H, H12-14), 1.30-1.16 (br. s, 18H, H12-23), 0.87 (br. s, 3H, H24);

^{13}C NMR (75 MHz, $CDCl_3$, δ (ppm)): 168.96 (C8), 164.93 (C3), 132.09 (C1), 127.95 (C2), 74.60 (C6), 51.34 (C11), 32.03 + 31.94 + 29.73 + 29.64 + 29.52 + 29.46 + 29.37 (Caliph.), 28.80 (C17-19), 24.79 + 22.81 (Caliph.), 14.24 (C24);

IR (neat): v (cm^{-1}) = 3305.1, 2954.1, 2914.8, 2848.9, 1731.1, 1659.5, 1557.8, 1470.9, 1403.6, 1365.5, 1294.8, 1260.6, 1223.9, 1181.6, 1127.0, 1090.0, 1070.9, 986.8, 942.0, 896.3, 807.1, 717.2, 656.4, 500.0, 404.3;

HRMS (FAB) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{38}NO_3$, 340.2853; found, 340.2852.

4.2.2 1-oxo-1-(pentylamino)octan-2-yl acrylate 2: Freshly distilled acrylic acid (20 mmol, 1 eq) and heptyl aldehyde (30 mmol, 1.5 eq) were mixed in 25 mL of ice cold dichloromethane. Under stirring, pentyl isocyanide (30 mmol, 1.5 eq) was added dropwise to the solution. The mixture was then stirred for 24 h at room temperature. Afterward, the mixture was concentrated under vacuum and purified *via* column chromatography (silica gel) yielding 90% of a yellow viscous liquid.

R_f = 0.52 (cyclohexane/ethyl acetate = 80/20, column gradient 95/5 - 80/20);

^{1}H NMR (300 MHz, $CDCl_3$; δ (ppm)): = 6.50 (dd, J = 17.3, 1.1 Hz, 1H, H1a), 6.20 (dd, J = 17.2, 10.4 Hz, 1H, H2), 6.00 (s, 1H, H10), 5.94 (dd, J = 10.4, 1.1 Hz, 1H, H1b), 5.27-5.21 (m, 1H, H6), 3.35-3.17 (m, 2H, H11), 1.96-1.77 (m, 2H, H7), 1.58-1.17 (m, 14H, H12 16,18 19), 1.28 (br, 12H, H13-16,18-19), 0.94-0.81 (m, 6H, H17,20);

^{13}C NMR (75 MHz, $CDCl_3$, δ (ppm)): 169.75 (C8), 164.97 (C3), 132.24 (C1), 127.85 (C2), 74.44 (C6), 39.33 (C11), 32.03 + 31.72 + 29.32 + 29.09 + 29.02 + 24.86 + 22.64 + 22.42 (C7,11-16,18-19), 14.13 + 14.07 (C17+20);

IR (neat): ν (cm^{-1}) = 3304.0, 2955.4, 2926.9, 2858.4, 1730.7, 1654.8, 1538.3, 1458.9, 1404.8, 1377.7, 1293.8, 1257.4, 1177.1, 1118.5, 1049.5, 982.4, 835.7, 808.4, 775.1, 725.3, 673.0;

HRMS (FAB) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{30}NO_3$, 284.2226; found, 284.2227.

4.2.3 1-(cyclohexylamino)-1-oxopropan-2-yl acrylate 3: Freshly distilled acrylic acid (20 mmol, 1 eq) and acetaldehyde (30 mmol, 1.5 eq) were mixed in 25 mL of ice cold dichloromethane. Under stirring, cyclohexyl isocyanide (30 mmol, 1.5 eq) was added dropwise to the solution. The mixture was then stirred for 24 h at room temperature. Afterward, the mixture was concentrated under vacuum and purified *via* column chromatography (silica gel) yielding 94% of a yellow solid.

R_f = 0.53 (cyclohexane/ethyl acetate = 60/40, column 60/40);

^{1}H NMR (300 MHz, $CDCl_3$, δ (ppm)): 6.45 (dd, J = 17.3, 1.3 Hz, 1H, H1a), 6.16 (dd, J = 17.3, 10.4 Hz, 1H, H2), 5.97 (d, J = 6.7 Hz, 1H, H10), 5.90 (dd, J = 10.4, 1.3 Hz, 1H, H1b), 5.22 (q, J = 6.8 Hz, 1H, H6), 3.81 – 3.66 (m, 1H, H11), 1.94 – 1.02 (m, 10H, H12-16), 1.46 (d, J = 6.8 Hz, 3H, H7);

^{13}C NMR (75 MHz, $CDCl_3$, δ (ppm)): 169.23 (C8), 164.64 (C3), 132.02 (C1), 127.73 (C2), 70.81 (C6), 48.21 (s), 32.97 (s), 25.14 (d, J = 57.8 Hz), 17.73 (s);

IR (neat): ν (cm^{-1}) = 3278.0, 3093.4, 2932.0, 2852.5, 1725.3, 1656.6, 1559.7, 1449.5, 1400.7, 1289.5, 1271.4, 1251.4, 1191.3, 1140.4, 1095.2, 1036.8, 989.9, 968.5, 891.2, 862.5, 810.8, 671.7, 437.9, 401.2;

HRMS (FAB) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{20}NO_3$, 226.1443; found, 226.1445.

4.3 General Procedure for the Polymerization in Solution

The respective acrylate monomer (2 mmol, 1 eq) and azobisisobutyronitrile (3.3 mg, 0.002 mmol, 0.01 eq) are dissolved in 2.20 mL of ethyl acetate. The solution is cooled with ice and subsequently degassed for 10 min with argon. Afterward, the mixture is stirred for 6 h at 70 °C under argon. The resulting polymer was purified by precipitation in cold methanol. After the precipitation, the polymer is two times centrifuged and washed. Afterward, the polymer is dried under vacuum.

4.4 General Preparation of Miniemulsions

Miniemulsions were prepared as follow if not stated otherwise. The respective amount of SDS was dissolved in 15 mL of deionized water. The S values used in the main text correspond to the surfactant to monomer weight ratio. Monomer (0.273 g), varying amounts of EGDMA, and 1.9mol% hexadecane (of the total amount of substance of the monomer, EGDMA, and cosolvent) were dissolved in 2 mL (1.732 g, 14.9 mmol) of tertbutyl acetate. The SDS solution was filtered and subsequently added to the organic solution. This mixture was then stirred for 1 h at room temperature. After pre-emulsification by stirring for 1 h, the mixture was ultrasonicated for 2 min at an amplitude of 60% with a Branson Digital Sonicator 250 equipped with an 0.5-inch tip. During sonication, the mixture was cooled with an ice bath.

4.5 Miniemulsion Polymerization Procedure

The miniemulsions were polymerized as follows if not stated otherwise. The freshly prepared miniemulsion was purged with argon for 10 min. Afterward, 5.5wt% (of the mass of the monomer and EGDMA) potassium peroxydisulfate was added under argon. The mixture was stirred for 3 h at 85 °C in a pre-heated oil bath under argon yielding the final microgel dispersion. The dispersion is subsequently dried by lyophilization (-50 °C, 10^{-3} mbar, 24 h) with a Christ Alpha 1-4. The products were stored at 24 °C.

4.6 Determination of Monomer/Crosslinker Conversion

The conversion of monomer and crosslinker was determined by gas chromatography-mass spectrometry (GC-MS). Thus, samples of the emulsion were taken directly after miniemulsification prior to the addition of potassium peroxydisulfate and after 6 h of polymerization time. Hexadecane served as the internal standard. GC-MS samples were prepared by evaporation of water, addition of ethyl acetate to dissolve contained monomer and crosslinker, and subsequent filtration to remove any insoluble parts. GC-MS chromatograms were recorded on a Varian 431 GC instrument with a capillary column FactorFour VF-5 ms (30 m × 0.25 mm × 0.25 mm) and a Varian 210 ion trap mass detector. Scans were performed from 40 to 650 m/z at a rate of 1.0 scans s^{-1}. The oven temperature program was: initial temperature 95 °C, hold for 1 min, ramp at 15 °C min^{-1} to 220 °C, hold for 4 min, ramp at 15 °C min^{-1} to 300 °C, hold for 2 min. The injector transfer line temperature was set to 250 °C. Measurements were performed in the split-split mode (split ratio 50:1) using helium as carrier gas (flow rate 1.0 mL min^{-1}).

4.7 DLS Measurements

Particle size distributions were determined by dynamic light scattering (DLS). For sample preparation, one drop of the respective miniemulsion was diluted in 10 mL water (if not stated otherwise) for at least 1 h. Size measurements were performed at a constant temperature (25 °C) in the respective solvent. Glass cuvettes were used. The equilibration time was set to 1 min. The particle size distributions displayed in this paper are an average calculated from eight subsequent measurements of which up to two highly deviating results were discarded. The experiments were performed on a Malvern Nanosizer S tabletop system with a He-Ne Laser (633 nm) and a scattering angle of 173 °.

4.8 Further Instrumentation

^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AVANCE DPK spectrometer at a frequency of 300 MHz and 75 MHz, respectively. For sample preparation, 10 – 15 mg of substance were dissolved in approximately 0.50 ml $CDCl_3$ (99.80atom% D) in an NMR-tube with a diameter of 5 mm. The chemical shift (δ) was given in parts per million (ppm) relative to δ of tetramethylsilane (δ(TMS) = 0.00 ppm).

The chemical shifts of $CDCl_3$ were used for referencing: ^{1}H-NMR: 7.26 ppm; ^{13}C-NMR: 77.16 ppm. Splitting patterns were denoted as follows: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), p (pentet), m (multiplet), and br (broad). The respective coupling constants *J* were given in Hertz (Hz).

IR spectra were recorded on a Bruker Alpha FTIR spectrometer equipped with Platinum ATR technology. The resulting transmittance spectra are averaged from 24 measurements. The energies of the IR bands were given in cm^{-1}.

High-resolution mass spectrometry was performed on a Finnigan MAT95 instrument *via* fast atom bombardment (FAB)

Size Exclusion Chromatography (SEC) was performed on a Shimadzu (LC-20A) equipped with a SIL-20A autosampler, precolumn PSS SDV (5 µm, 8 x 50 mm), main-column PSS DDV analytical 10000 A (5 µm, 8 x 300 mm) and a RID-10A refractive index detector in tetrahydrofuran (flow rate 1 mL min^{-1}) at 50 °C. The calibration was performed relative to PMMA standards. Samples were prepared by dissolution of 2 mg of dried polymer material in 2 mL of tetrahydrofuran and subsequent filtration.

Atomic Force Microscopy (AFM) was performed on a Bruker Dimension Icon under nitrogen atmosphere in a glove box. The samples were imaged using a RTESPA-tip in tapping mode.

The sample was scanned in a 90 °-angle with a scanning frquency of 0.5 Hz. Samples were prepared by 100-fold dilution of the polymer dispersion.

4.9 Density Functional Theory (DFT)

The LogP values were calculated by DFT (using ORCA with BP86 hybrid functional[47] and a high quality def2-SVP basis set[48] together with the Grimme method to describe the Van der Walls interactions [49,50] and the universal solvatation model[51].

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

Acknowledgements

The authors thank Tobias Leonhard for the imaging of the microgels *via* AFM and Etienne Grau for the DFT calculations.

Received: ((will be filled in by the editorial staff))

Revised: ((will be filled in by the editorial staff))

Published online: ((will be filled in by the editorial staff))

References

[1] W. O. Baker, *Ind. Eng. Chem.* **1949**, *41*, 511.

[2] H. Staudinger, W. Heuer, E. Husemann, I. J. Rabinovitch, *Trans. Faraday Soc.* **1936**, *32*, 323.

[3] B. R. Saunders, N. Laajam, E. Daly, S. Teow, X. Hu, R. Stepto, *Adv. Colloid Interface Sci.* **2009**, *147-148*, 251.

[4] R. Pelton, *Adv. Colloid Interface Sci.* **2000**, *85*, 1.

[5] J. A. Bonham, M. A. Faers, J. S. van Duijneveldt, *Soft Matter* **2014**, *10*, 9384.

[6] B. Sharma, S. Striegler, *Biomacromolecules* **2018**, *19*, 1164.

[7] G. Agrawal, R. Agrawal, *Small* **2018**, *14*, e1801724.

[8] D. Klinger, K. Landfester, *Polymer* **2012**, *53*, 5209.

[9] M. Reufer, P. Díaz-Leyva, I. Lynch, F. Scheffold, *Soft Matter* **2009**, *28*, 165.

[10] F. Candau, Y. S. Leong, R. M. Fitch, *J. Polym. Sci. Polym. Chem. Ed.* **1985**, *23*, 193.

[11] S. Schachschal, A. Balaceanu, C. Melian, D. E. Demco, T. Eckert, W. Richtering, A. Pich, *Macromolecules* **2010**, *43*, 4331.

[12] Y.-B. Kim, H.-K. Kim, J.-W. Hong, *Suf. Coat. Technol.* **2002**, *153*, 284.

[13] S. V. Vinogradov, T. K. Bronich, A. V. Kabanov, *Adv. Drug Delivery Rev.* **2002**, *54*, 135.

[14] F. Scheffold, P. Díaz-Leyva, M. Reufer, N. Ben Braham, I. Lynch, J. L. Harden, *Phys. Rev. Lett.* **2010**, *104*, 128304.

[15] K. Kratz, T. Hellweg, W. Eimer, *Polymer* **2001**, *42*, 6631.

[16] S.-G. Kim, Y.-G. Seo, Y.-J. Cho, J.-S. Shin, S.-C. Gil, W.-M. Lee, *Bull. Korean Chem. Soc.* **2010**, *31*, 1891.

[17] A. Biffis, N. B. Graham, G. Siedlaczek, S. Stalberg, G. Wulff, *Macromol. Chem. Phys.* **2001**, *202*, 163.

[18] D. Saatweber, B. Vogt-Birnbrich, *Prog. Org. Coat.* **1996**, *28*, 33.

[19] D. Crespy, K. Landfester, *Beilstein J. Org. Chem.* **2010**, *6*, 1132.

[20] J. M. Asua, *Prog. Polym. Sci.* **2002**, *27*, 1283.

[21] K. Landfester, N. Bechthold, S. Förster, M. Antonietti, *Macromol. Rapid Commun.* **1999**, *20*, 81.

[22] K. Fontenot, F. J. Schork, *Ind. Eng. Chem. Res.* **1993**, *32*, 373.

[23] K. Landfester, N. Bechthold, F. Tiarks, M. Antonietti, *Macromolecules* **1999**, *32*, 5222.

[24] K. Landfester, M. Willert, M. Antonietti, *Macromolecules* **2000**, *33*, 2370.

[25] L. Ouyang, L. Wang, F. J. Schork, *Macromol. Chem. Phys.* **2010**, *211*, 1977.

[26] Z. Cao, U. Ziener, K. Landfester, *Macromolecules* **2010**, *43*, 6353.

[27] A. Llevot, A. C. Boukis, S. Oelmann, K. Wetzel, M. A. R. Meier, *Top. Curr. Chem.* **2017**, *375*, 66.

[28] B. Yang, Y. Zhao, Y. Wei, C. Fu, L. Tao, *Polymer Chemistry* **2015**, 6, 8233.

[29] R. Kakuchi, *Angew. Chem. Int. Ed.* **2014**, 53, 46.

[30] U. Tunca, *Macromol. Chem. Phys.* **2018**, 219, 1800163.

[31] L. Xia, Z. Zhang, Y.-Z. You, *Polym. J.* **2020**, 52, 33.

[32] J. Wang, A. Qin, B. Z. Tang, *Macromol. Rapid Commun.* **2021**, 42, 2000547.

[33] B. T. Tuten, C. Barner-Kowollik, *Macromol. Rapid Commun.* **2021**, 42, 2000495.

[34] K.-Y. Yoon, G. Dong, *Macromol. Rapid Commun.* **2021**, 42, 2000646.

[35] I. Ugi, A. Dömling, W. Hörl, *Endeavour* **1994**, *18*, 115.

[36] A. Sehlinger, O. Kreye, M. A. R. Meier, *Macromolecules* **2013**, *46*, 6031.

[37] J.-M. Noy, M. Koldevitz, P. J. Roth, *Polym. Chem.* **2015**, *6*, 436.

[38] S. Schmidt, M. Koldevitz, J.-M. Noy, P. J. Roth, *Polym. Chem.* **2015**, *6*, 44.

[39] Q. Zhang, Y. Zhang, Y. Zhao, B. Yang, C. Fu, Y. Wei, L. Tao, *ACS Macro Lett.* **2015**, *4*, 128.

[40] M. von Czapiewski, K. Gugau, L. Todorovic, M. A.R. Meier, *Eur. Polym. J.* **2016**, *83*, 359.

[41] Q. Sun, G. Liu, H. Wu, H. Xue, Y. Zhao, Z. Wang, Y. Wei, Z. Wang, L. Tao, *ACS Macro Lett.* **2017**, *6*, 550.

[42] T. Mao, G. Liu, H. Wu, Y. Wei, Y. Gou, J. Wang, L. Tao, *J. Am. Chem. Soc.* **2018**, *140*, 6865.

[43] M. Passerini, *Gazz. Chim. Ital.* **1921**, *51*, 126.

[44] A. Dömling, I. Ugi, *Angew. Chem. Int. Ed.* **2000**, *39*, 3168.

[45] Y. Pei, J.-M. Noy, P. J. Roth, A. B. Lowe, *Polym. Chem.* **2015**, *6*, 1928.

[46] K. Landfester, *Top. Curr. Chem.* **2003**, *227*, 75.

[47] F. Neese, F. Wennmohs, U. Becker, C. Riplinger, *The Journal of Chemical Physics* **2020**, 152, 224108.

[48] F. Weigend, R. Ahlrichs, *PCCP* **2005**, 7, 3297.

[49] S. Grimme, S. Ehrlich, L. Goerigk, *J. Comput. Chem.* **2011**, 32, 1456.

[50] S. Grimme, J. Antony, S. Ehrlich, H. Krieg, *The Journal of Chemical Physics* **2010**, 132, 154104.

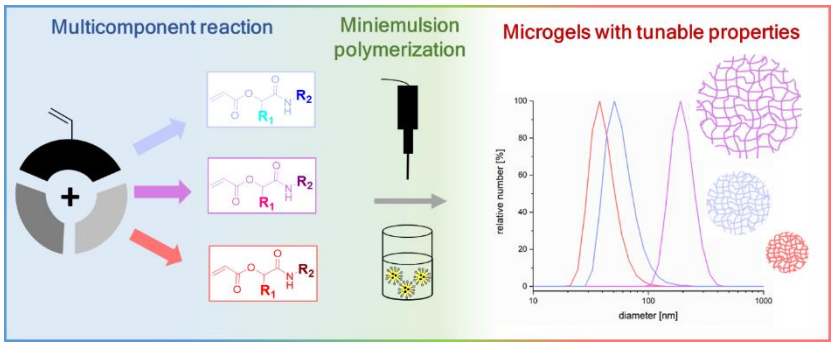
[51] A. V. Marenich, C. J. Cramer, D. G. Truhlar, *The Journal of Physical Chemistry B* **2009**, 113, 6378.

The table of contents entry

Microgels from three acrylate monomers are synthesized *via* miniemulsion polymerization. The particle size is tuned between 21 nm and 91 nm. The dependence of the surfactant concentration, crosslinker concentration, and the sonication time and amplitude is investigated. The acrylate monomers are synthesized with yields up to 94 % using the Passerini-three-component reaction.

*Julian Tobias Windbiel, Audrey Llevot,**

Microgel Preparation by Miniemulsion Polymerization of Passerini Multicomponent Reaction Derived Acrylate Monomers



Supporting Information

Microgel Preparation by Miniemulsion Polymerization of Passerini Multicomponent Reaction Derived Acrylate Monomers

*Julian Tobias Windbiel, Audrey Llevot,**

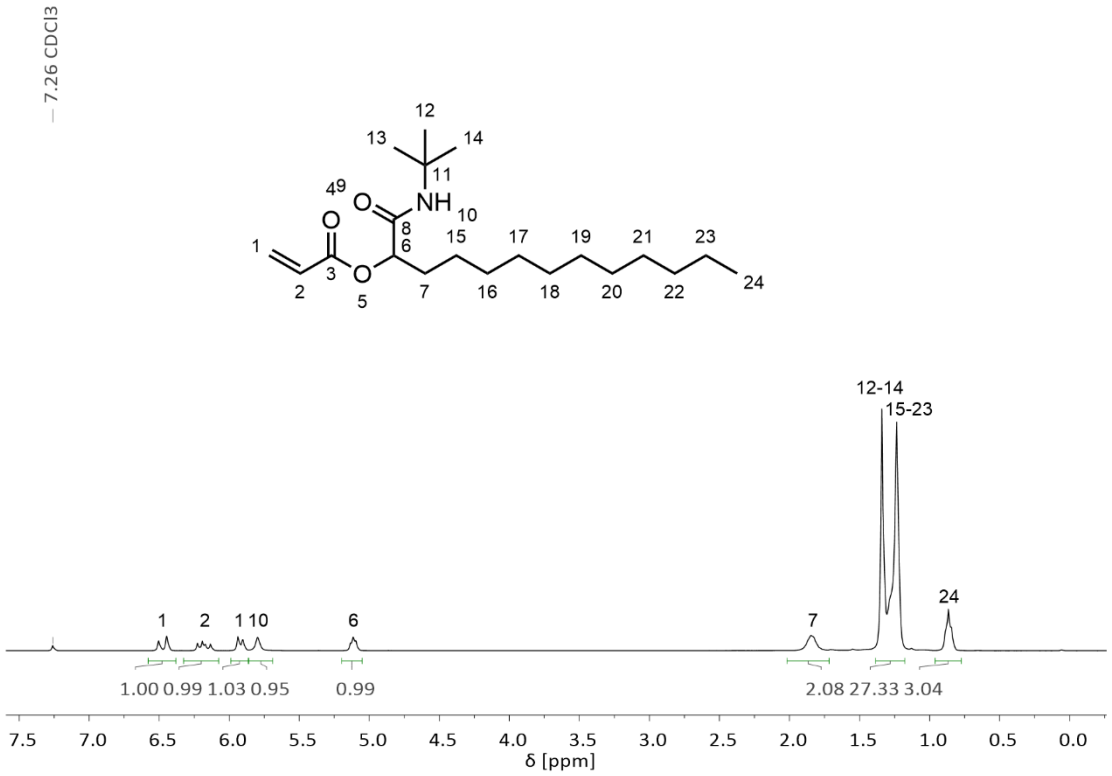


Figure S1 ^{1}H-NMR in $CDCl_3$ of monomer 1.

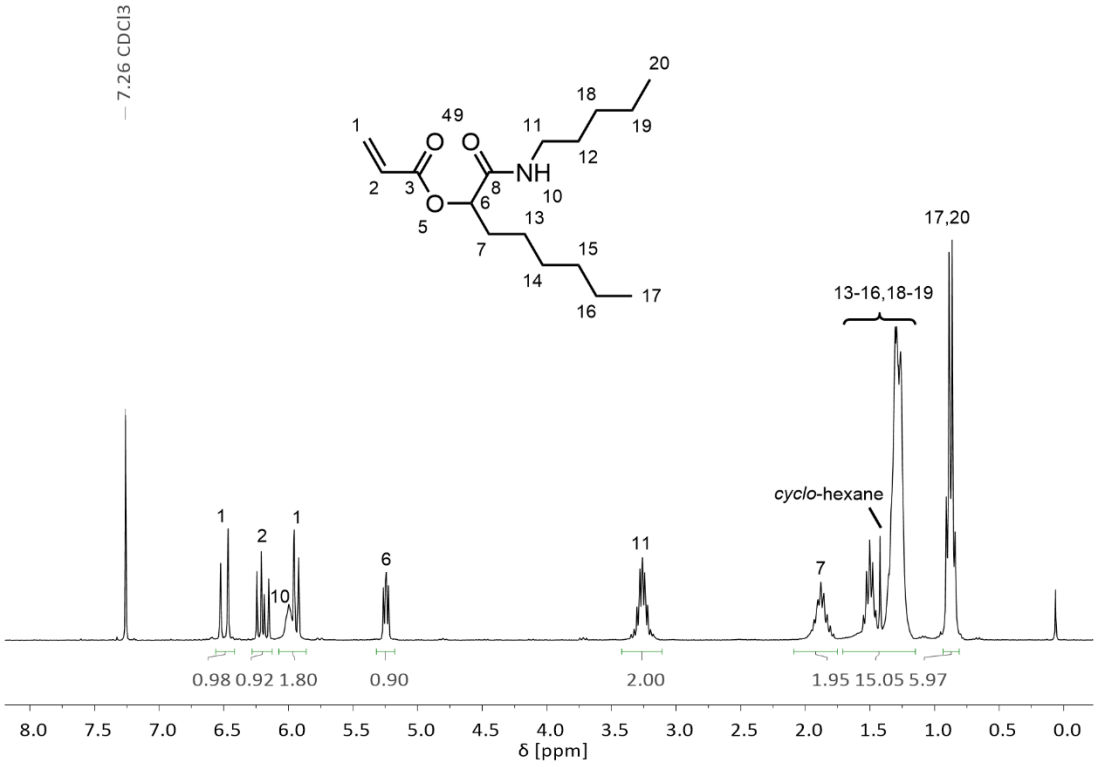


Figure S2 ^{1}H-NMR in $CDCl_3$ of monomer 2.

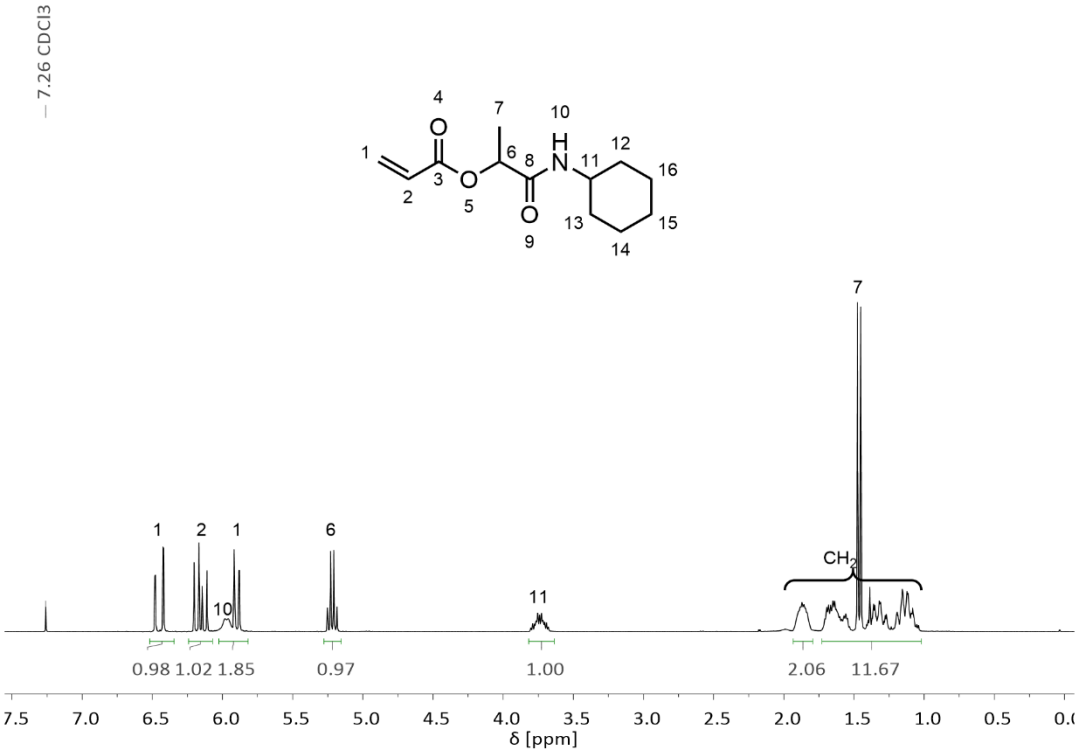


Figure S3 ^{1}H-NMR in $CDCl_3$ of monomer 3.

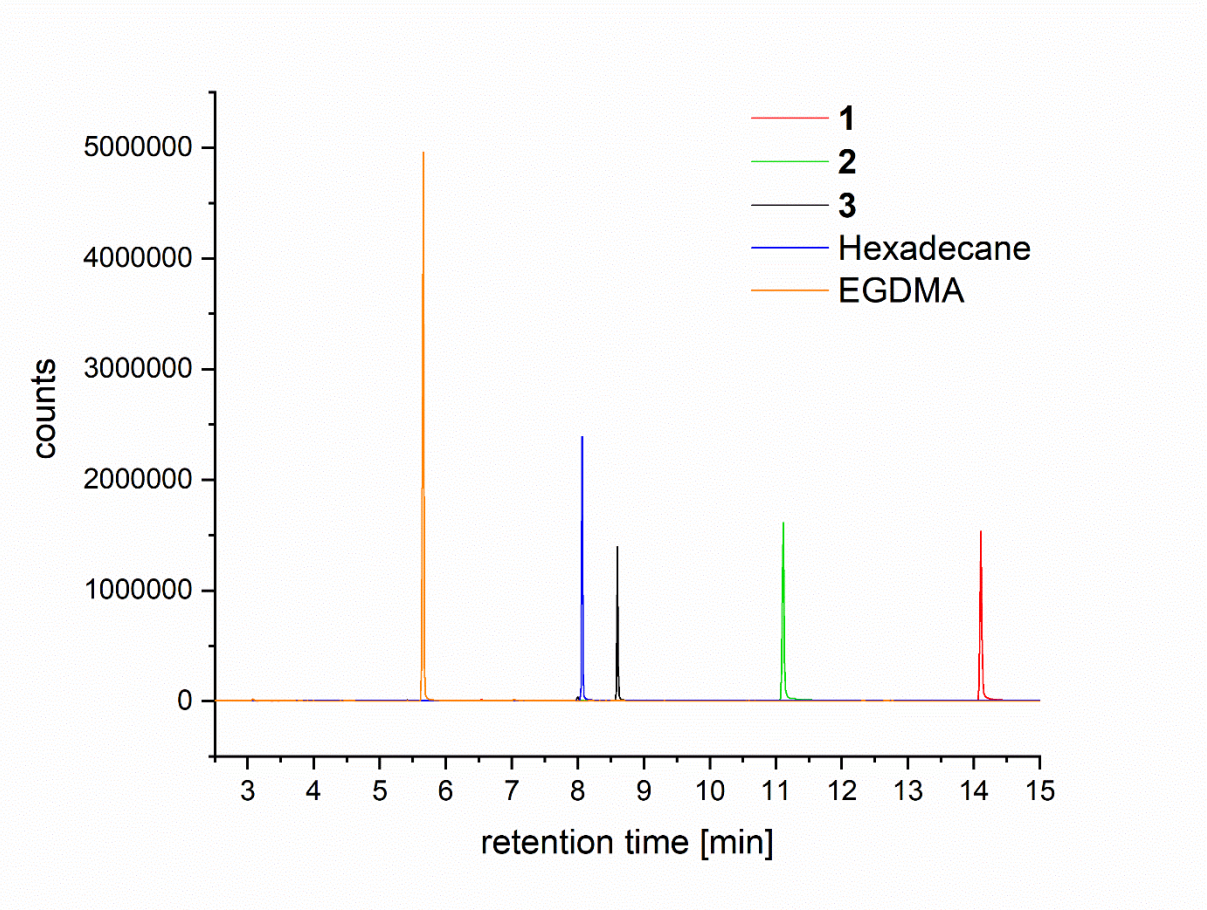


Figure S4 GC-MS chromatogram of the monomers **1**-**3** as well as hexadecane and EGDMA.

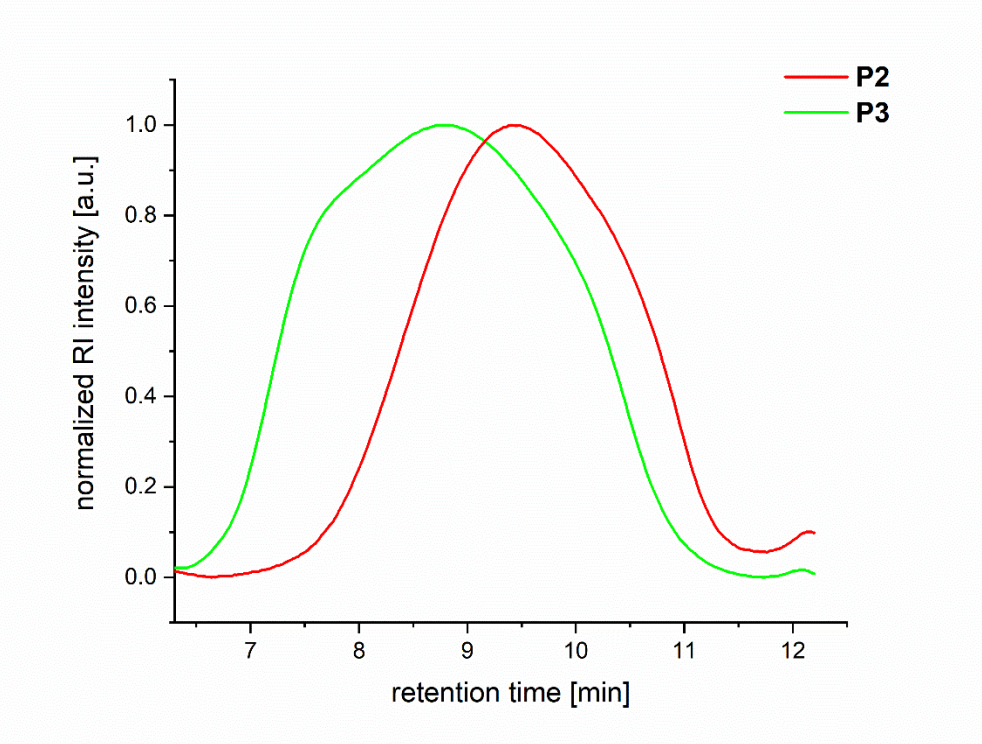


Figure S5 Normalized SEC-chromatograms of P**2** and **P3**.

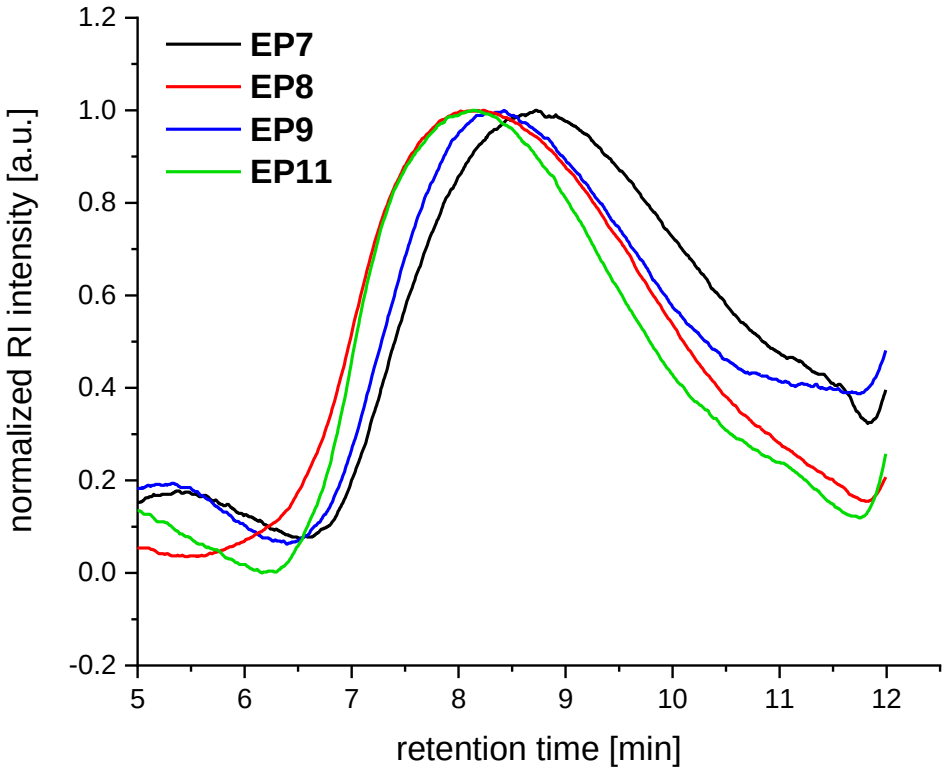


Figure S6 Normalized SEC-diagram of EP7-9 and EP11.

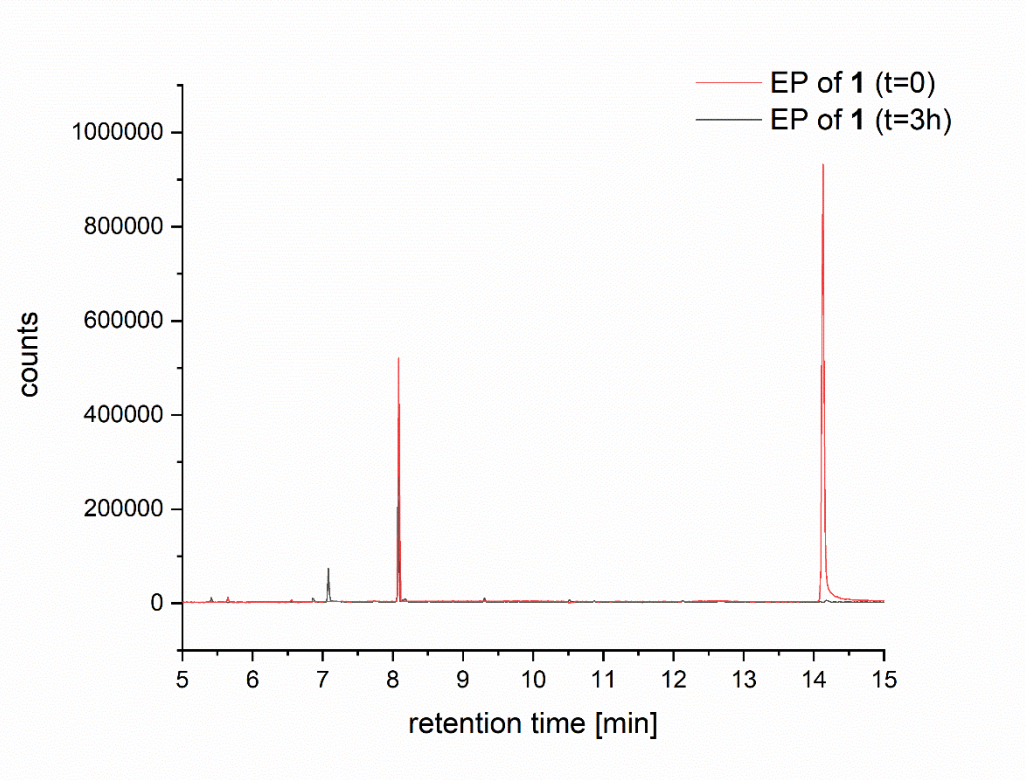


Figure S7 GC-MS chromatogram of the miniemulsion polymerization of **1**.

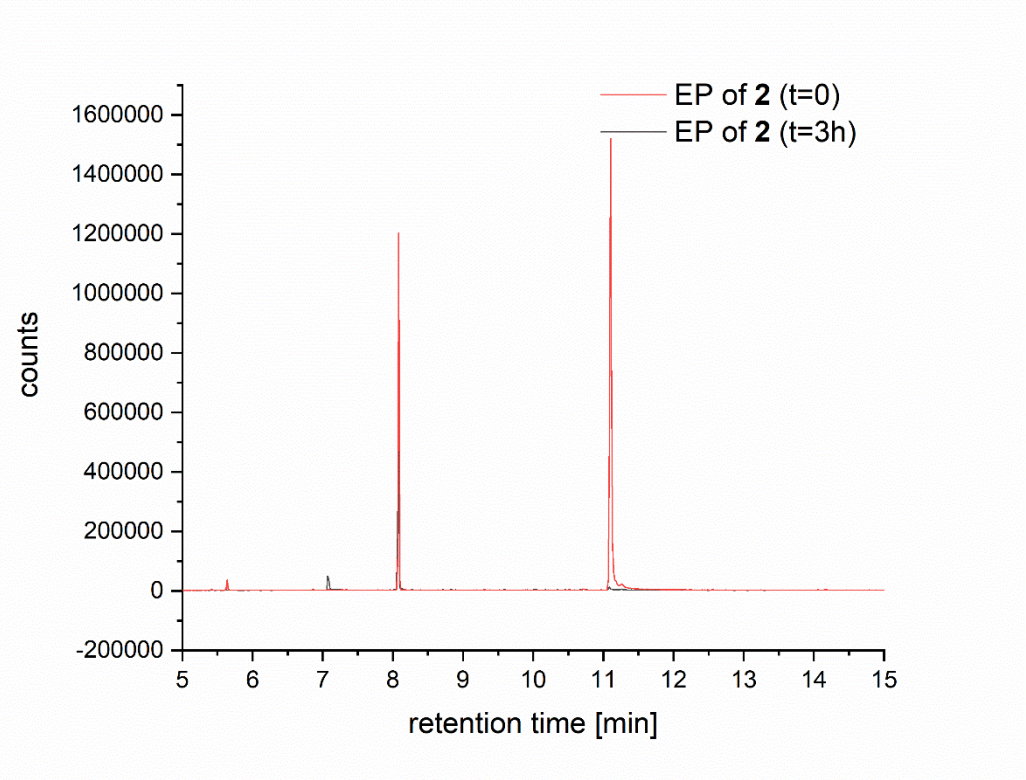


Figure S8 GC-MS chromatogram of the miniemulsion polymerization of **2**.

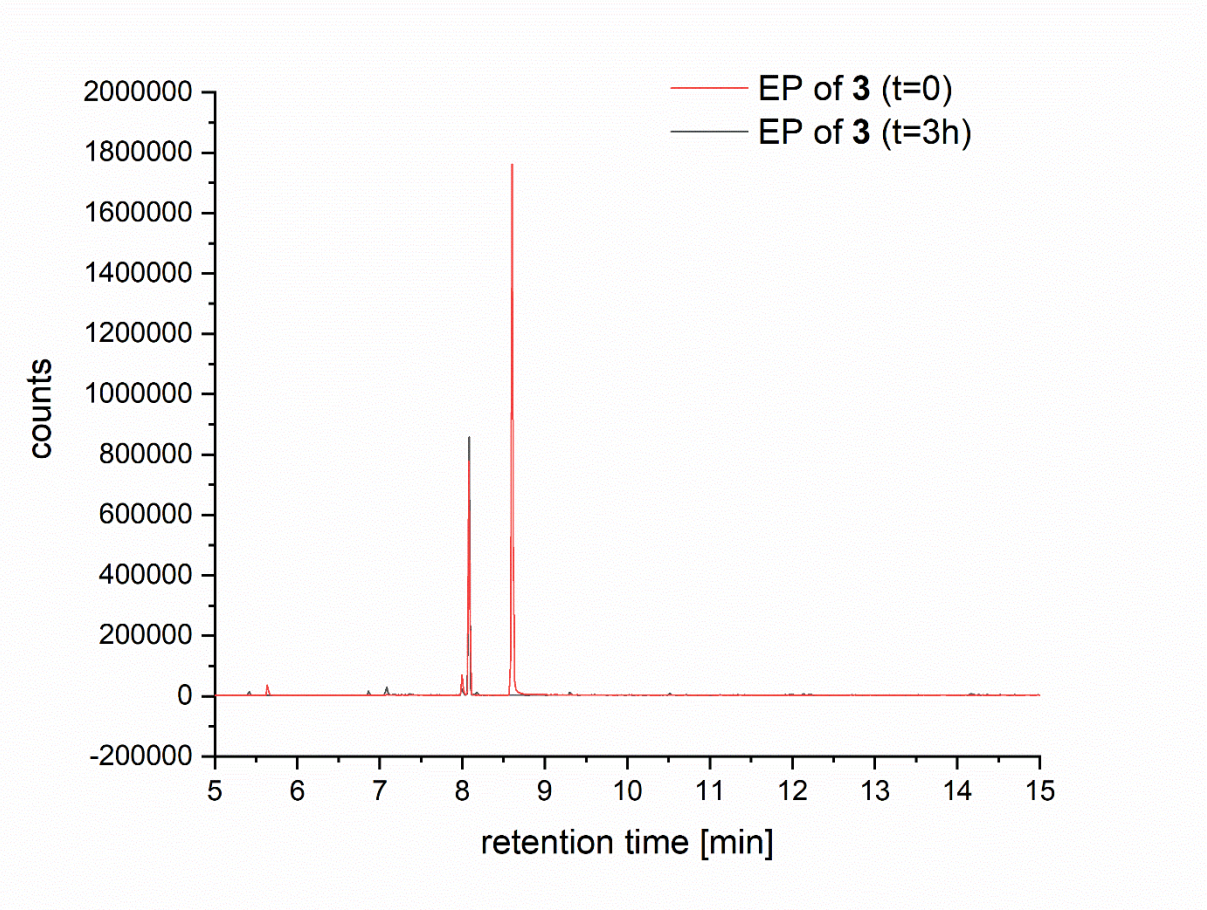


Figure S9 GC-MS chromatogram of the miniemulsion polymerization of **3**.

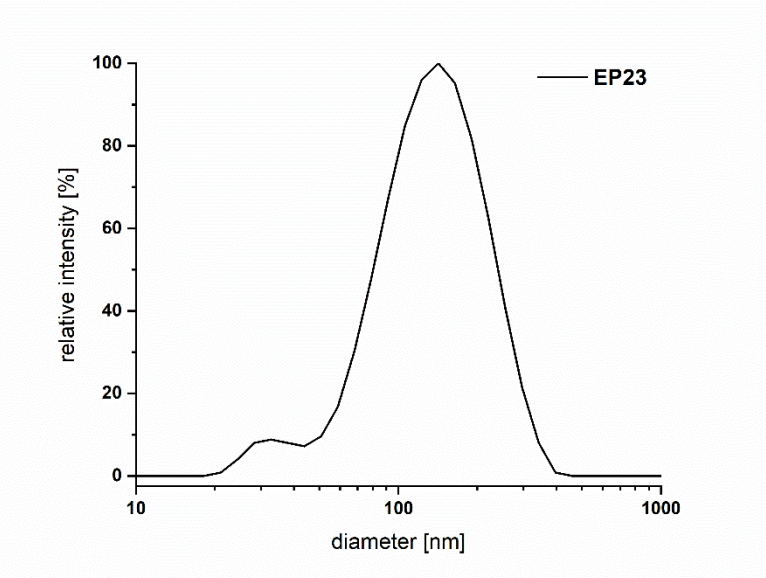
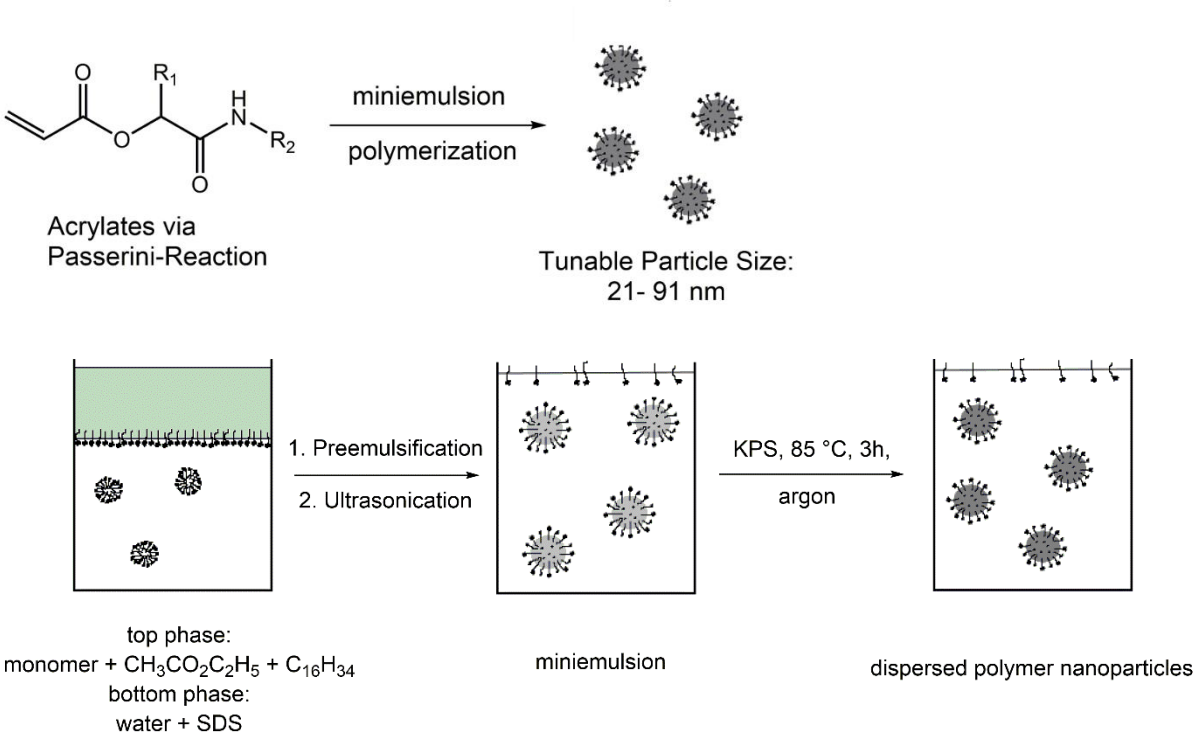


Figure S10 Intensity distribution of **EP23** measured by DLS.



Scheme S1 Preparation method for the production of nanoparticles in miniemulsion.

Table S1 DLS results of non-crosslinked particles synthesized from monomer **1** depending on sonication time, amplitude, and surfactant concentration.

Emulsion polymerization	Amplitude [%]	Sonication time [min]	*S*	*d* [nm]	*PDI*
EP1	60	0.5	0.010	44	0.181
EP2	60	1	0.010	44	0.182
EP3	60	2	0.010	44	0.162
EP4	30	2	0.010	44-51	0.185
EP5	60	2	0.010	44	0.162
EP6	100	2	0.010	38	0.188
EP7	60	2	0.002	91	0.081
EP8	60	2	0.005	59	0.133
EP9a[b)]	60	2	0.010	44	0.153
EP10	60	2	0.010	44	0.162
EP11	60	2	0.100	33	0.147

[a)]reproduction of **EP3**

Table S2 SEC results of EP7-9 and EP11.

Emulsion polymerisation	*S*	M_n [kg mol^{-1}]	M_w [kg mol^{-1}]	*Đ*
EP7	0.002	39.0	243.6	6.4
EP8	0.005	63.7	516.5	5.1
EP9	0.010	81.2	468.2	5.8
EP11	0.100	73.3	449.0	6.1