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Supporting Information

# Transformer-Induced Metamorphosis of Polymeric Nanoparticle Shape at Room Temperature

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## Materials

4-cyano-4-[(ethylsulfanylthiocarbonyl)sulfanyl]pentanoic acid (ECT, 95%) was procured from ABCR. All the other chemicals were purchased from Sigma Aldrich. The AIBN was recrystallized in methanol before use. A membrane with molecular weight cut-off of 3.5 kDa was utilized for dialysis. Deionized water was utilized for all experiments.

## Instrumentations

**$^1$H nuclear magnetic resonance ($^1$H-NMR)** spectra were measured in deuterated solvents on a Bruker Avance-300 spectrometer. Chemical shifts are given in ppm and are referenced to residual solvent proton signals.

**Size-exclusion chromatography (SEC)** was measured on Shimadzu equipment with a CBM-20A system controller, a SIL-20A automatic injector, an LC-20AD pump (flow rate at 1 mL $min^{-1}$), a 10.0 µm bead-size guard column (50 × 7.5 mm) followed by three KF-805L columns (300 × 8 mm, bead size: 10 µm, pore size maximum: 5000 Å), an SPD-20A ultraviolet detector, and a RID-20A differential refractive index detector. Column temperature was maintained at 40 °C using a CTO-20A oven. *N*,*N*-dimethylacetamide was used as eluent (HPLC grade, Acros, with 0.03% w/v LiBr). Molecular weights were determined according to calibration with commercial narrow molecular weight distribution poly(methyl methacrylate)

standards with molecular weights ranging from 5000 to $1.5 \times 10^6$ g $mol^{-1}$ (Agilent Technology). Before injection, all samples were passed through 0.45 µm filters and water was removed by drying sample under air (only for nanoemulsion experiments).

**Transmission electron microscopy (TEM)** images were taken without staining for polystyrene and with Uryl acetate staining (2% concentrated in aqueous, 30 seconds) for methacrylate using Jeol JEM 1400 (High Voltage: 80 kV, 120 kV, Emitter: LaB6 crystal) transmission electron microscope. TEM samples were prepared as follows: 2 µL of latex were diluted in 200 µL of deionized water and a droplet was put onto a carbon film grid (300 Mesh, Cu, Electron Microscopy Science), after which samples were allowed to dry under ambient atmosphere and temperature.

**Cryogenic electron microscopy** (Cryo-EM) images were taken on a 120 kV Tecnai Spirit G2 (FEI) TEM under low dose utilizing a 2k x 2k UltraScan CCD camera. Samples were prepared for cryo-EM using a Vitrobot (Thermo Fisher). Briefly, 3 µL of sample was placed on a glow-discharged Quantifoil R 3.5/1 holey carbon grid within a humidified chamber at 4 °C, blotted for 3 seconds with a blotting force of -3 before being plunged into liquid ethane. Vitrified samples were transferred to liquid nitrogen for storage prior to imaging.

**Dynamic light scattering (DLS)** measurements were carried out using a Malvern Zetasizer Nano Series ZS, employing a backscatter detection system at 173 °C angle and a standard laser (4 mW, 633 nm) or using Malvern Zetasizer Advance

Series-Pro (Red Label, 10 mW, 633 nm). The sample refractive index (RI) was set at 1.59 for styrene and 1.49 for methyl methacrylate latexes. The dispersant viscosity and RI were set to 0.89 Ns $m^{-2}$ and 1.33, respectively. To determine particle size, all measurements were carried out without dilution whereas solutions were diluted ten times before running zeta potential analysis.

**SAXS**

SAXS measurements were employed to confirm that the assigned morphologies remained unaltered in solution. Experiments were performed on a Rigaku SAXS instrument with a MicroMax-002+ microfocused beam that was operated at a voltage and filament current of 45 kV and 0.88 mA, respectively. The Ni-filtered Cu $K_\alpha$ radiation ($\lambda_{CuK\alpha}$=1.5418 Å) was collimated by three pinholes (0.4, 0.3 and 0.8 mm) and the data were collected with a two-dimensional argon-filled Triton detector. An effective scattering-vector range of 0.05 $Å^{-1} < q < 0.2$ $Å^{-1}$ was probed, where q is the scattering wave vector defined as $q=4\pi\sin(\theta)/\lambda_{CuK\alpha}$, with a scattering angle of 2θ, calibrated using silver behenate. Quartz glass capillaries with 2 mm of diameter, containing the samples were placed onto a stainless-steel holder, and the samples were measured for 30 minutes. The scattering signal of a capillary filled with water was subtracted from the measurements as a background correction, after normalizing based on sample X-ray transmission and measurement time. We measured each sample after a few hours to confirm that

the morphologies remained stable over time. We used sphere, worm and vesicle form factor models to determine the slopes of the scattering curves.[1]

## Procedures

### 1.1 Synthesis of P(DEGMA-*co*-HPMA)

As previously described,[2] di(ethylene glycol) methyl ether methacrylate (DEGMA) (3.5 g, 18.6 mmol, 40 equiv.),4-cyano-4-[(ethylsulfanylthiocarbonyl)sulfanyl] pentanoic acid (ECT) (122.6 mg, 0.5 mmol, 1 equiv.), 2-hydroxypropyl methacrylamide (HPMA) (1.33 g, 9.3 mmol, 20 equiv.), and 4,4'-azobis(4-cyanovaleric acid) (ACPA) (10.5 mg, 0.4 mmol, 0.1 equiv.) were dissolved in dimethyl sulfoxide (DMSO) (20 mL) and placed in a 25 mL round bottom flask, equipped with a stirring bar. Upon degassing the solution with $N_2$ for 40 min, the flask was placed in a preheated oil bath (70 °C) at 300 rpm. After 8.5 hours, the reaction was quenched by cooling it down in an ice bath and exposing it to air. The polymerization was sample to determine DEGMA and HPMA conversion by $^1$H-NMR. The solution was then dialyzed against acetone for 1 hour to remove DMSO from the solution. Then, the solution was precipitated in a mixture of petroleum ether: diethyl ether (1: 1, v/ v), isolated by centrifugation, and re-dissolved in acetone. This step was repeated three times to remove unreacted monomers. The

product was dried in a vacuum oven for 48 hours and analyzed by SEC and $^{1}$H-NMR.

### 1.2 RAFT emulsion polymerization of styrene using P(DEGMA-*co*-HPMA) as macro-CTA

P(DEGMA-*co*-HPMA) macro-CTA (25 mg, 0.003 mmol, 1 equiv.) was added in a 15 mL glass Schlenk tube, equipped with a stirring bar. Then it was dissolved with an aqueous solution of sodium dodecyl sulfate (SDS), which is below the CMC and it stabilizes the macro-CTA via hydrophobic interaction, (0.5 mg of SDS in 2 mL of deionized water, 0.0017 mmol, 0.6 equiv.) prior degassing with $N_2$ for 25 min. Upon deoxygenation the Schlenk tube was immersed in a preheated oil bath at 70 $^{o}$C for 5 min, and the emulsion was formed. In parallel, a stock solution containing a mixture of styrene and azobisisobutyronitrile (AIBN) was prepared in a 2 ml glass vial (2.5 mg of AIBN dissolved in 500 ul of styrene) and degassed for 5 minutes with nitrogen. It is noted that the choice of a hydrophobic free radical initiator, such as AIBN is important as it would be presented in the core of the particles together with the styrenic monomer thus allowing the decomposed AIBN radicals to immediately react with styrene and initiate the polymerization inside the nanoparticles. Subsequently, 50 µl of this solution (AIBN, 0.25 mg, 0.002 mmol, 0.5 equiv., styrene, 0.435 mmol, 150 equiv.) was transferred into the preformed emulsion, and the reaction was conducted for 4.5 hours at 70 $^{o}$C under continuous stirring at 500 rpm. Polymerization was stopped by exposing the solution to air and

analyzed by $^{1}$H NMR, SEC and DLS to determine the conversion (97 %), molecular weight/dispersity ($M_n$ = 14300, $Đ$= 1.30), and the size of emulsion spheres (main distribution at 1100 nm with PDI= 0.49). The solution was kept at 70 $^{o}$C, under stirring, for 5 hours in order for any remained monomer to be evaporated.

### 1.3 Morphological transformation of P((DEGMA-*co*-HPMA)-*b*-styrene)

An aliquot (100 μL) of the final latex synthesized according to procedure 1.2 was transferred in a glass vial. Then, 0.5 μl of toluene ($m_{toluene}/m_{PS}$= 0.19*) was added and the dispersion was shaken upside down for 30 seconds resulting in the formation of wormball like particles (main distribution at 1400 nm with PDI= 1). To obtain the next morphology, in the same vial, an extra 1 μl of toluene ($m_{toluene}/m_{PS}$= 0.57) was added and the wormball shaped particles transformed into worm-like particles. Finally, a further addition of 3.5 μl toluene ($m_{toluene}/m_{PS}$= 1.91), induced the formation of vesicles like particles (main distribution at 1700 nm with PDI= 0.63). It is noted that the macro-CTA is trapped in glassy PS and only released in water when toluene is added to decrease the particle viscosity.

*For the calculation of the weight ratio of transformer over the core-forming block, the following formula was used: $\mathbf{m_{styrene} = V_{styrene} \times d_{styrene} \rightarrow m_{Polystyrene} = m_{styrene} \times conversion,}$

$\mathbf{m_{toluene} = V_{toluene} \times d_{toluene.}}$ $\mathbf{d_{styrene} = 0.909\ gr/ml,\ d_{toluene} = 0.867\ gr/ml.}$

## 2.1 Synthesis of poly(glycerol monomethacrylate) (PGMA)

To begin, the monomer glycerol monomethacrylate (GMA) was obtained following literature.[3] Glycidyl methacrylate (GlyMA, 5.00 g) and deionized water (45.0 g) were added to a round-bottomed flask, equipped with a stirring bar. The initial aqueous emulsion was stirred overnight at 85 °C in an oil bath, using a condenser. The initial emulsion became a homogeneous aqueous solution with a quantitative conversion of GlyMA to GMA. In a second time, the previous solution of GMA (25.0 g of an ~11.2% w/w 2.8 g, 17.5 mmol GMA) and 4-((((2-carboxyethyl)thio)carbonothioyl)thio)-4-cyanopentanoic acid (CECPA) (0.259 g, 0.7 mmol) were added in a round bottom flask equipped with a stirring bar. Then, this solution was heated at 50 °C for 2 min, in order for the CECPA to be fully dissolved. Next, the solution was cooled down to room temperature and the pH was lowered to 2.5–3.0 by adding a 37 % aqueous solution of HCl, before the addition of VA-044 (18.9 mg, 0.07 mmol) as water soluble radical initiator. Upon degassing the reaction mixture with $N_2$ for 30 minutes, the reaction was heated up to 50 °C for 4 hours. Finally, the reaction was quenched by exposing it to air and cooling it down in an ice bath. Samples were taken to determine the monomer conversion (99%) by $^1$H-NMR using methanol-$d_4$ and molecular weight and dispersity ($M_n$ = 9900, $Đ$= 1.14) via SEC.

## 2.2 Aqueous PISA of GlyMA using PGMA as macro-CTA

PGMA macro-CTA obtained according to procedure 2.1 (1 g of stock solution, 0.112 g PGMA, 2.7 x $10^{-2}$ mmol (based on $^1$H NMR), 1 equiv.), GlyMA (0.129 g,

0.91 mmol, 34 equiv.), VA-044 (0.813 mg, 3 x $10^{-2}$ mmol, 0.1 equiv.) and water (0.85 g) were introduced in a 5 ml glass vial, equipped with a stirring bar. Then, to maintain the pH at 2.5/3, an 37 % aqueous solution of HCl was added. Upon deoxygenation with $N_2$, for 30 minutes in an ice bath, the solution was transferred in a preheated oil bath (50 $^{o}$C) to conduct the polymerization. After 2 hours, the reaction was stopped by exposing the solution to air and analyzed by $^{1}$H NMR, SEC and DLS to determine the conversion (99 %), molecular weight/dispersity

($M_n$ = 14500, $Đ$= 1.21), and the size of spheres (main distribution at 12 nm with PDI= 0.04).

### 2.3 Morphological transformation of P(GMA-*b*-GlyMA)

An aliquot (200 µL) of the final solution (spherical nanoparticles) synthesized according to procedure 2.2 was transferred in a glass vial. Then, 12 µl of GlyMA ($m_{GlyMA}/m_{PGlyMA}$= 0.93*) was added and the dispersion was shaken upside down for 30 seconds resulting in free standing gel of worm like particles. To obtain the next morphology, in the same vial, an extra 18 µl of GlyMA ($m_{GlyMA}/m_{PGlyMA}$= 2.34) was added and the worm shaped particles transformed into vesicle like particles and the solution became again fluid (main distribution at 104 nm with PDI= 0.32). For the calculation of the weight ratio of transformer over the core-forming block, the following formula was used:

**$m_{GlyMA} = V_{GlyMA}$ x $d_{GlyMA}$ -> $m_{PolyGlyMA} = m_{GlyMA}$ x conversion, $m_{GlyMA} = V_{GlyMA}$ x $d_{GlyMA}$. $d_{GlyMA}$=1.075 gr/ml**

### 3.1 Synthesis of P(POEGMA)

Poly(ethylene glycol) methyl ether methacrylate ($POEGMA_{300}$) (2 g, 6.7 mmol, 30 equiv.), 4-cyanopentanoic acid dithiobenzoate (CPADB) (62 mg, 0.22 mmol, 1 equiv.), and AIBN (3.6 mg, 0.022 mmol, 0.1 equiv.) were dissolved in DMSO (10 mL) in a 25 mL round bottom flask, equipped with a stirring bar. Upon degassing the solution, with $N_2$ for 40 min, the flask was placed in a preheated oil bath (70 °C) under stirring (300 rpm), for 3 hours. In order to quench the reaction, the solution was cooled down in an ice bath, exposed to air and analyzed by $^1$H NMR, and SEC to determine the conversion (61 %), molecular weight/dispersity ($M_n$ = 6700, $Đ$= 1.09). The solution was then dialyzed against acetone for 3 hours to remove DMSO from the solution. Then, the solution was precipitated in a mixture of petroleum ether: diethyl ether (1:1, v/ v), isolated by centrifugation, and re-dissolved in acetone. This step was repeated three times to remove unreacted monomers. [4]

### 3.2 Organic PISA of styrene

P(POEGMA) macro-CTA (100 mg, $M_n$ ~ 8700, 1.14 x $10^{-2}$ mmol (based on $^1$H NMR)), styrene (5.93 g, 57 mmol), AIBN (0.19 mg, 1.14 x $10^{-3}$ mmol), and methanol (7.6 ml) were added to round bottom flask. Then, the reaction mixture was equally distributed over 5 vials (2.7 ml each) which were degassed with $N_2$, for 30 minutes in an ice-bath. After deoxygenation, the vials were placed in an oil bath at 70 °C. The reaction was quenched after 12 hours by rapid cooling and exposure to air and the conversion was calculated via $^1$H NMR (3.4%) and molecular

weight/dispersity via SEC ($M_n$ = 17400, $Đ$= 1.30). The polymers were purified by dialysis against methanol and the solvent was changed three times to remove all unreacted monomer. Next the dialysis was continued, for 2 days, with water to exchange the solvent.[3]

### 3.3 Morphological transformation of P(POEGMA-*b*-styrene)

An aliquot (100 μL) of the final solution synthesized according to procedure 3.2 was transferred in a glass vial. Then, 0.2 μl of toluene ($m_{toluene}/m_{PS}$= 0.44) was added and the dispersion was shaken upside down for 30 seconds resulting in the formation of the first intermediate octopi-like shape particles. To obtain the next morphology, in the same vial, an extra 0.1 μl of toluene ($m_{toluene}/m_{PS}$= 0.87) was added and the octopi-like shape shaped particles transformed into jellyfish like particles. Finally, a further addition of 0.1 μl toluene ($m_{toluene}/m_{PS}$= 1.31), induced the formation of vesicles like particles (main distribution at 169 nm with PDI= 0.25). For the calculation of the weight ratio of transformer over the core-forming block, the following formula was used: $\mathbf{m_{styrene} = V_{styrene} \times d_{styrene} \rightarrow m_{Polystyrene} = m_{styrene} \times conversion}$, $\mathbf{m_{toluene} = V_{toluene} \times d_{toluene}}$. $\mathbf{d_{styrene}}$ **=0.909 gr/ml**, $\mathbf{d_{toluene}}$**=0.867 gr/ml.**

### 4. Solution self-assembly

For the solution self-assembly, a water dispersion of P(POEGMA-b-styrene) worms was freeze dried. Next, the dried polymer was dissolved in acetone (a good solvent for both blocks) resulting in homogeneous solution (30 mg in 2 ml of acetone 0.15 wt %). In order to induce the self-assembly, water, a poor solvent for the core forming block, was fed into the acetone polymer solution with a rate of 1

ml per hour. Slowly, the solution started becoming turbid and the feeding of water was stopped after 20 hours (10 times more water compared to the initial acetone solution). Finally, to remove acetone, the dispersion was dialyzed against water for one day. Upon analyzing a sample from the final solution, by TEM, worm-like particles were observed. For the morphological transformation, toluene (0.8 µl) was added in 100 µl of the polymer dispersion. The turbidity of the solution increased almost immediately and the resulted morphology was analyzed via TEM, showing the formation of vesicles.

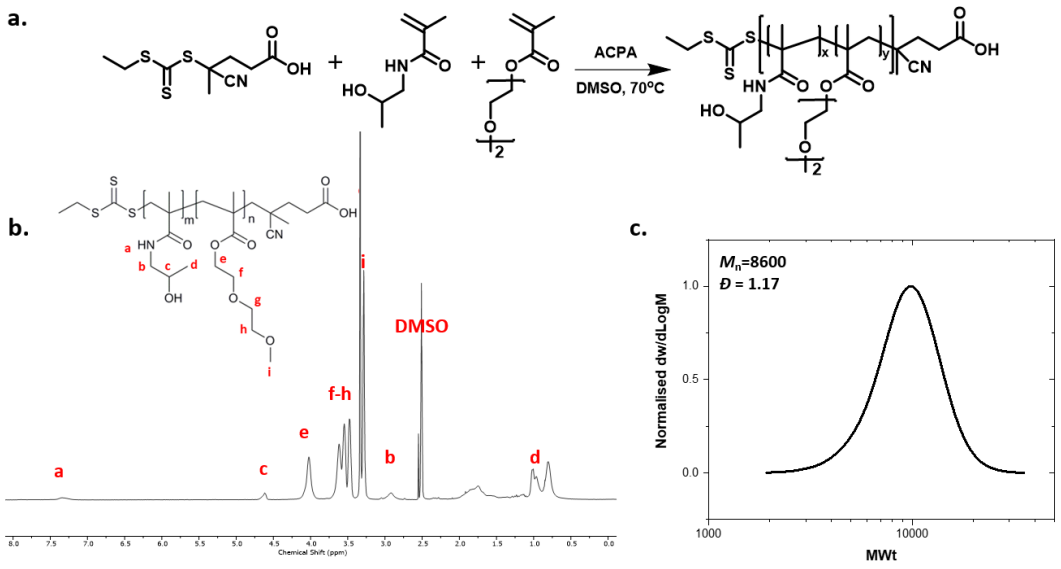


***Figure S1***: a) Chemical scheme of P(DEGMA-*co*-HPMA) synthesis, b) $^1$H NMR spectrum of purified P(DEGMA-*co*-HPMA) measured in DMSO-$d_6$ and c) SEC analysis of the P(DEGMA-*co*-HPMA).

| *Macro-CTA without SDS* | | |
|---|---|---|
| Temperature (°C) | *Macro-CTA without SDS* | |
| | Number (nm) | Error |
| 20 | 3.5 | 0.1 |
| 25 | 3.5 | 0.3 |
| 30 | 3.5 | 0.1 |
| 35 | 4 | 0.07 |
| 36 | 4 | 0.23 |
| 37 | 1197 | 213 |
| 38 | 2034 | 389 |
| 39 | 4000 | 616 |
| 40 | 4440 | 91 |
| 50 | 4300 | 1300 |
| 60 | 2200 | 942 |
| 70 | 1400 | 309 |

| *Macro-CTA with SDS* | | |
|---|---|---|
| Temperature (°C) | Macro-CTA with SDS | |
| | Number (nm) | Error |
| 20 | 2.7 | 0.68 |
| 25 | 3.4 | 0.9 |
| 30 | 3.5 | 0.1 |
| 35 | 2.5 | 0.06 |
| 36 | 2.7 | 0.7 |
| 37 | 2.5 | 0.1 |
| 38 | 2 | 0.15 |
| 39 | 1.9 | 0.7 |
| 40 | 1.8 | 0.25 |
| 41 | 2.7 | 0.63 |
| 42 | 1500 | 99 |
| 43 | 1473 | 245 |
| 44 | 1421 | 118 |
| 47 | 1685 | 124 |
| 50 | 1151 | 55 |
| 60 | 1341 | 37 |
| 70 | 1382 | 85 |

***Table S1:*** Lower critical solution temperature (LCST) characterization of P(DEGMA-*co*-HPMA) macro-CTA in the absence and presence of SDS, measured via DLS.

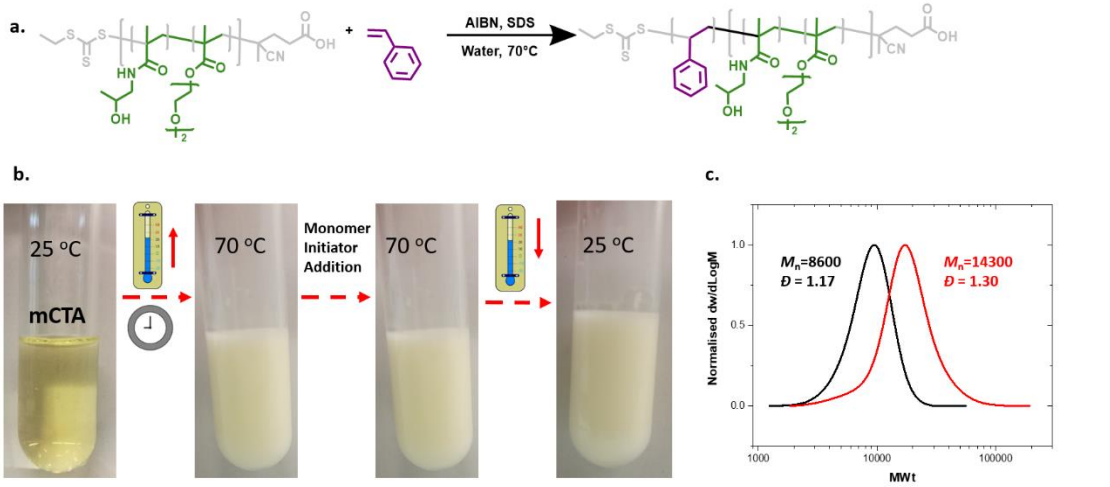


***Figure S2***: a) Chemical scheme of P((DEGMA-*co*-HPMA)-b-styrene) synthesis, b) optical representation of the emulsion polymerization procedure and c) SEC analysis of P(DEGMA-*co*-HPMA) (left trace) and P((DEGMA-*co*-HPMA)-*b*-styrene) (right trace).

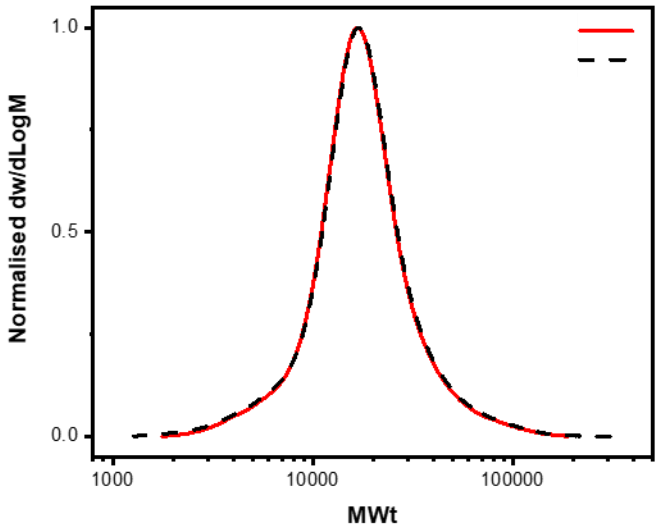


***Figure S3***: SEC characterization of P((DEGMA-*co*-HPMA)-*b*-styrene) emulsion spheres after 4.5 hours of polymerization (Red) and after exposing the latex into air for 5 hours at 70 $^{o}$C (Black).


| Formulation | Temperature | DLS data | | | | |
|---|---|---|---|---|---|---|
| | | Intensity (nm) | Volume (nm) | Number (nm) | Z-average | PDI |
| SDS | *70$^{o}$C* | 1014 (83%), 126 (7%) | 1180 (92%), 116 (2%) | 782 (2%), 99(97%) | 611 | 0.54 |
| | *25$^{o}$C* | 1024 (79%) 124 (20%) | 1180 (91%), 116(10%) | 899 (2%) 102 (98%) | 465 | 0.58 |

***Figure S4***: DLS and TEM characterization of P((DEGMA-*co*-HPMA)-*b*-Styrene) emulsion spheres at 25 and 70 $^{o}$C.

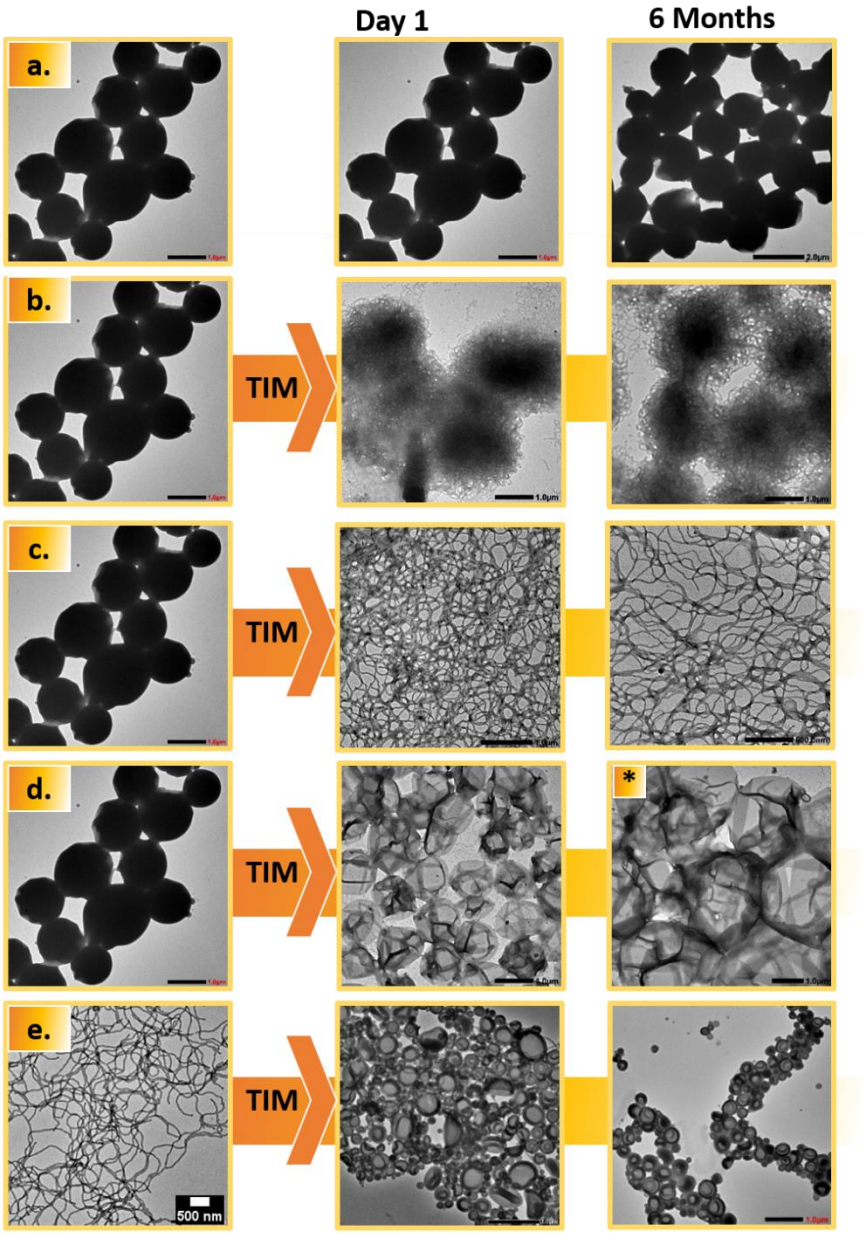


***Figure S5***: Stability study of nanoparticles formed via TIM: a. P((DEGMA-*co*-HPMA)-*b*-Styrene) emulsion spheres, b) P((DEGMA-*co*-HPMA)-*b*-Styrene) wormballs, c) P((DEGMA-*co*-HPMA)-*b*-Styrene) worms, d) P((DEGMA-*co*-HPMA)-*b*-Styrene) vesicles and d) P(POEGMA-*b*-styrene) vesicles. * The stability of P((DEGMA-*co*-HPMA)-*b*-Styrene) vesicles was studied for 4 days.

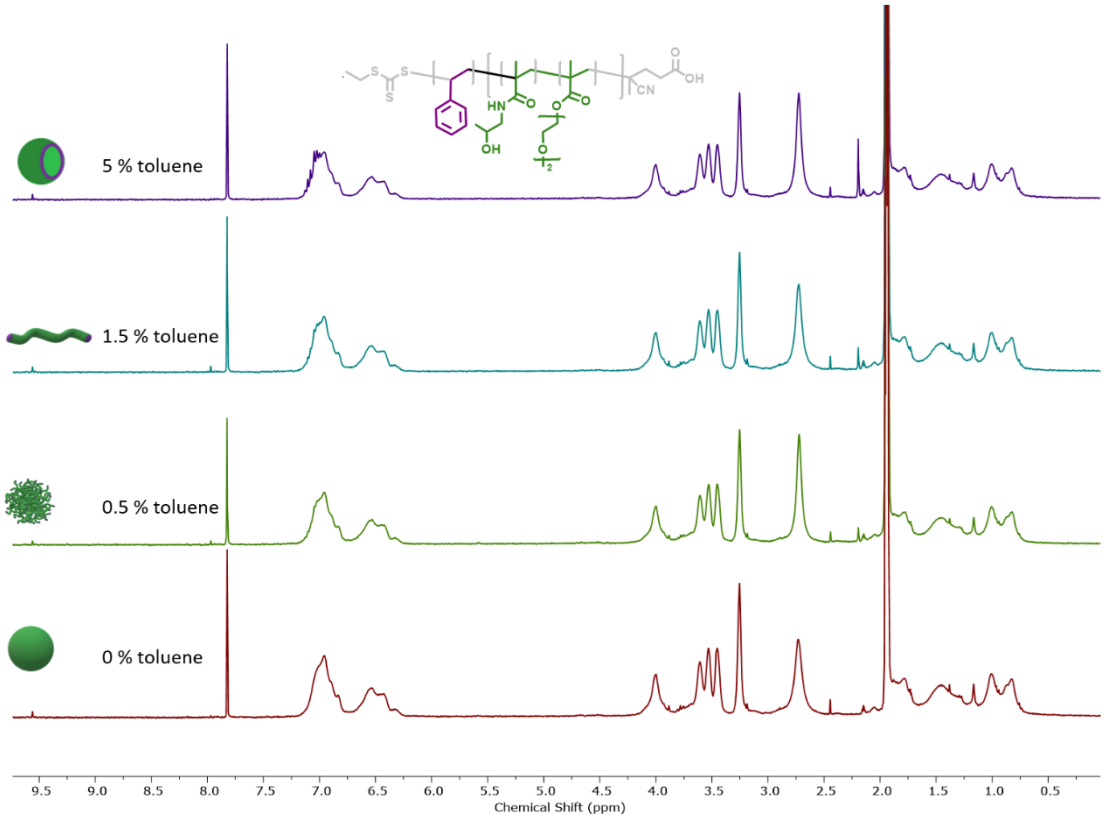


***Figure S6***: $^{1}$H NMR spectra of P((DEGMA-*co*-HPMA)-*b*-styrene) after addition of different amounts of toluene to obtain different morphologies. The water dispersions of the polymeric nanoparticles were dried via air purging in order to eliminate the amount of water. The spectra were measured in a mixture of acetone-$d_6$: chloroform-d in a 5:1 ratio.

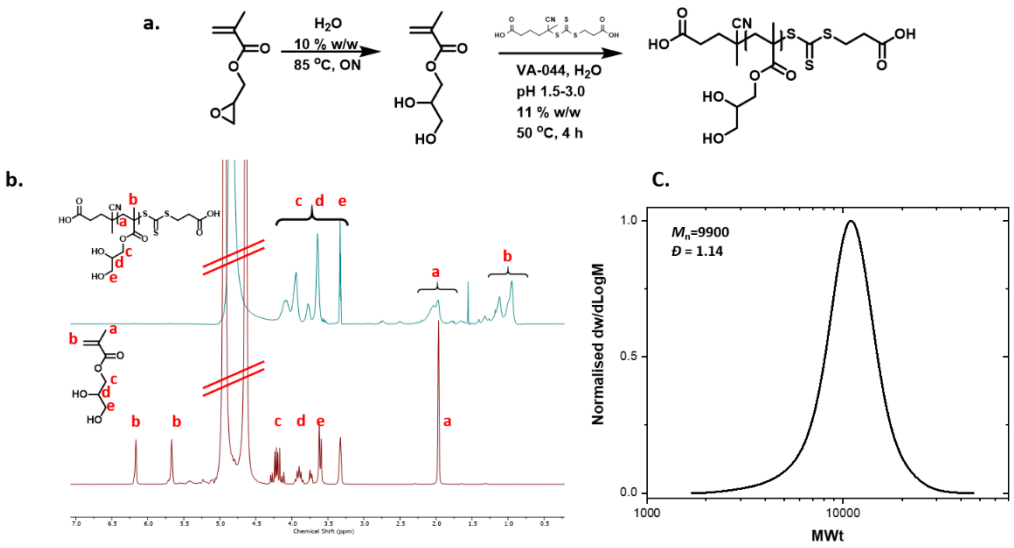


***Figure S7***: a) Chemical scheme of GMA (first step) and PGMA (second step) synthesis, b) $^{1}H$ NMR spectra of GMA (bottom) and PGMA (top) measured in methanol-$d_4$ and c) SEC analysis of PGMA.

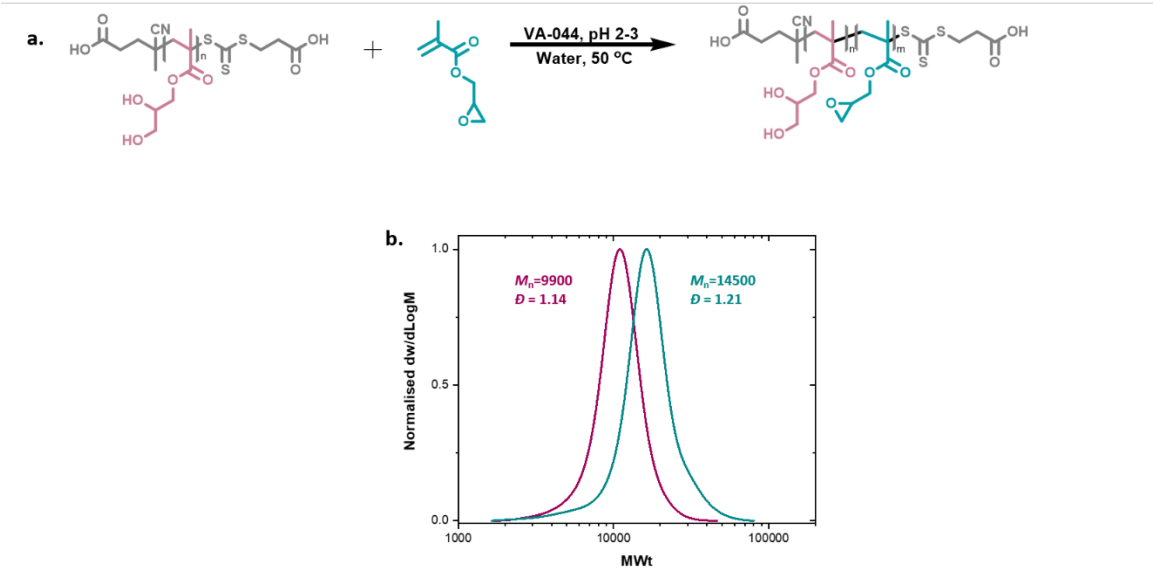


***Figure S8***: a) Chemical scheme of P(GMA-*b*-GlyMA) synthesis and b) SEC analysis of PGlyMA (left trace) and P(GMA-*b*-GlyMA) (right trance).

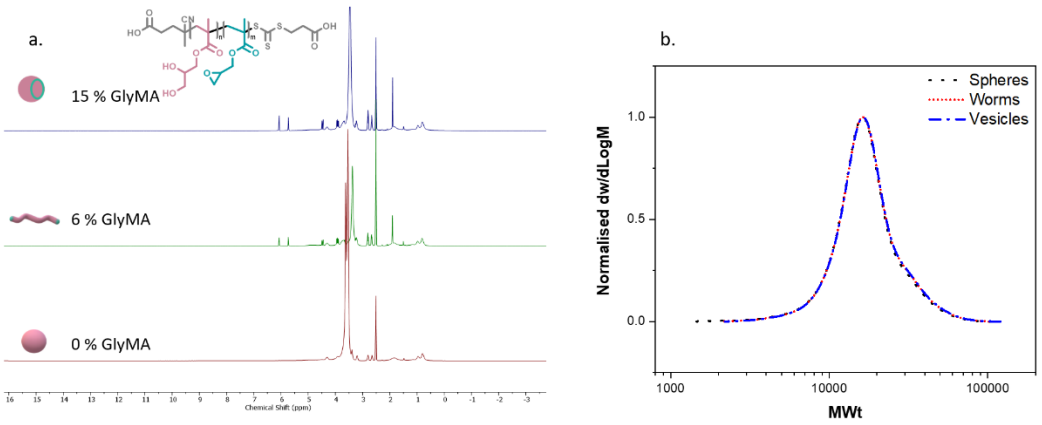


***Figure S9***: a) $^{1}$H NMR spectra of P(GMA-*b*-GlyMA), measured, after addition of different amounts of GlyMA to obtain different morphologies. The water dispersions of the polymeric nanoparticles were dried via air purging in order to eliminate the amount of water. The spectra were measured in a methanol-$d_4$ and b) SEC traces of P(GMA-*b*-GlyMA) after addition of different amounts of GlyMA to obtain different morphologies. SEC analysis was conducted without water removal.

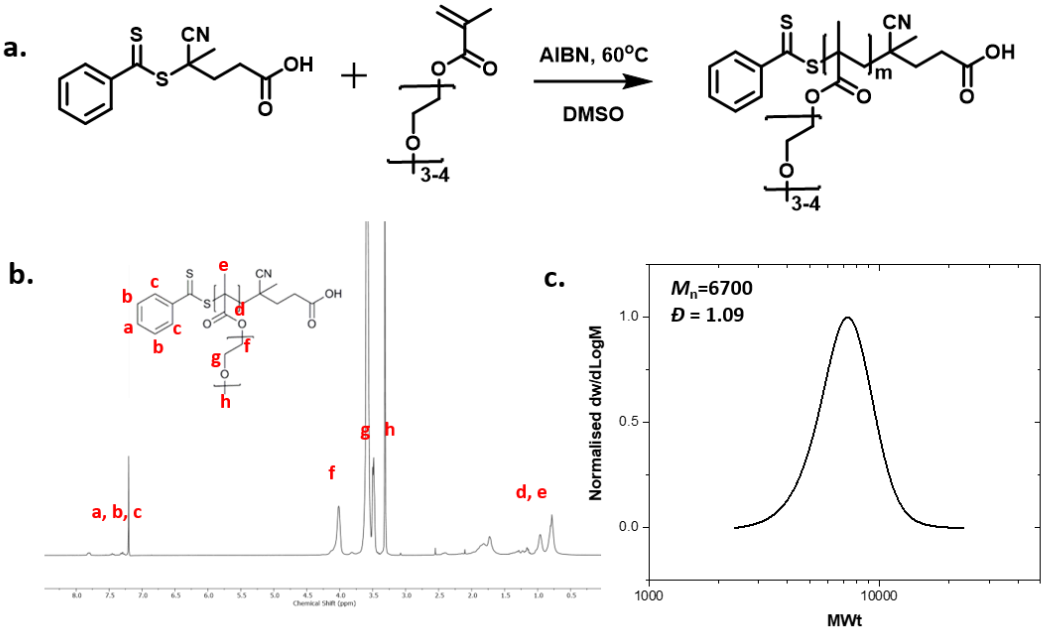


***Figure S10***: a) Chemical scheme of P(POEGMA) synthesis, b) $^{1}$H NMR analysis of purified P(POEGMA) measured in chloroform-d and c) SEC analysis of P(POEGMA).

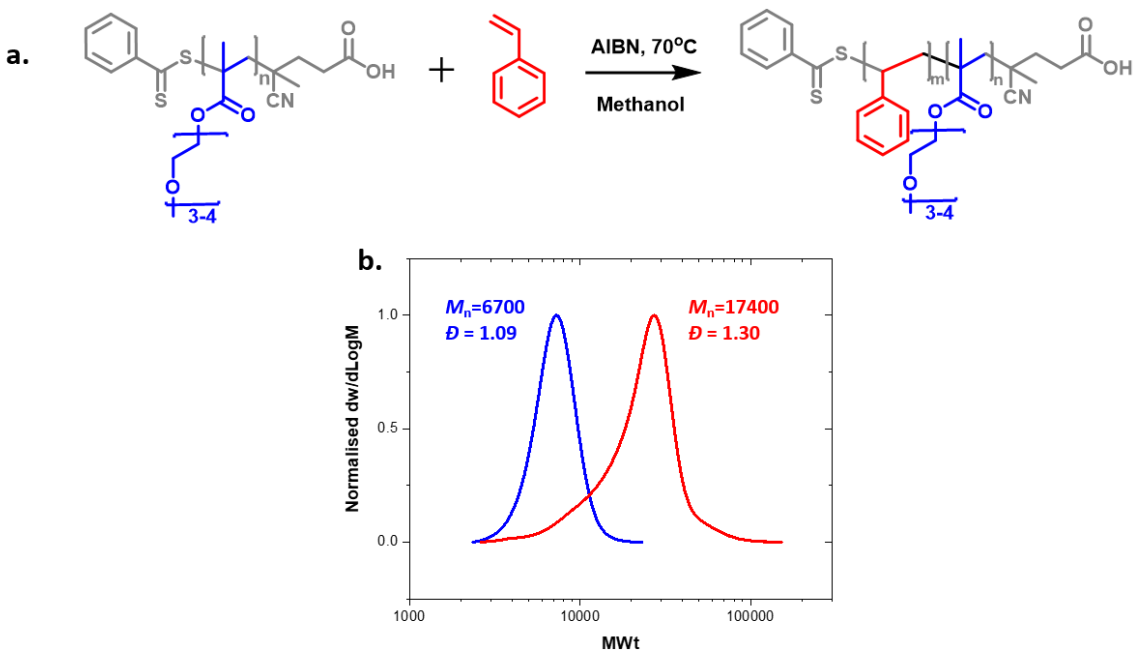


***Figure S11***: a) Chemical scheme of P(POEGMA-*b*-styrene) synthesis and b) SEC analysis of P(POEGMA) (left trace) and P(POEGMA-*b*-styrene) (right trace).

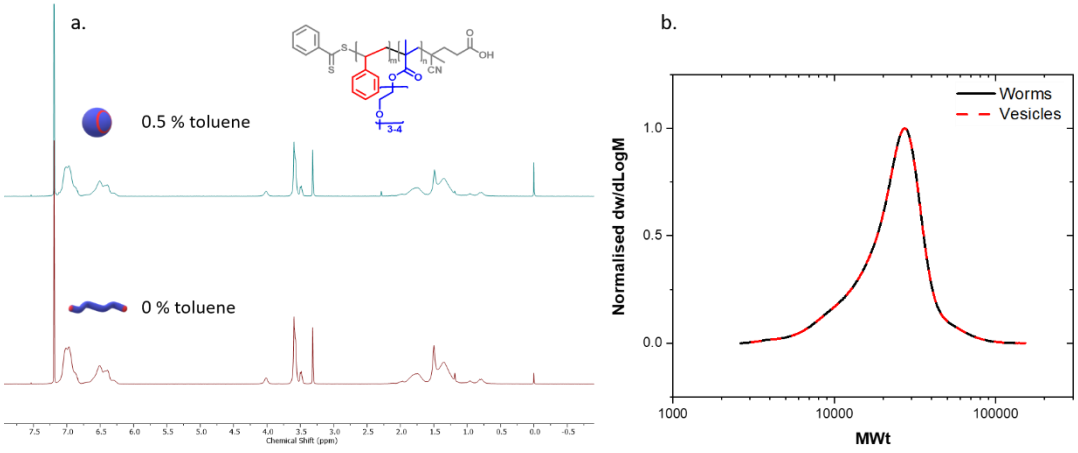


***Figure S12***: a) $^1$H NMR spectra of P(POEGMA-*b*-styrene) with (top spectrum) and without (bottom spectrum) addition of toluene. The water dispersions of the polymeric nanoparticles were dried via air purging in order to eliminate the amount of water. The $^1$H NMR spectra were recorded in chloroform-d, and b) SEC traces of P(POEGMA-*b*-styrene) before and after addition of toluene. SEC analysis was conducted without water removal.

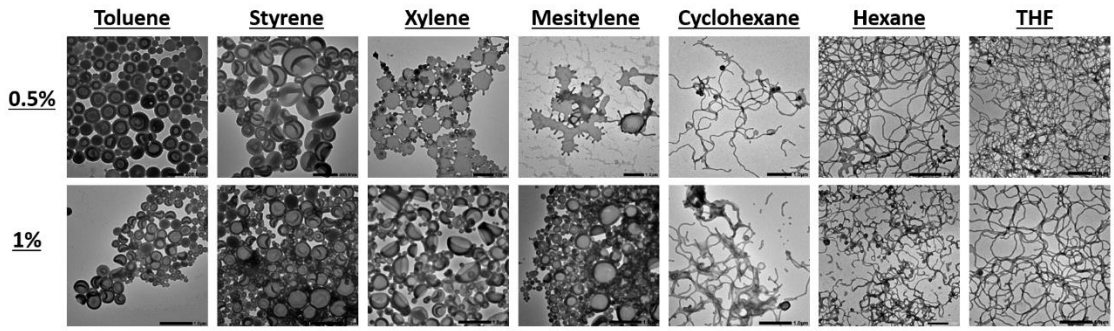


***Figure S13***: Addition of different organic molecules into P(POEGMA-*b*-styrene) worm-like nanoparticles/water dispersion.

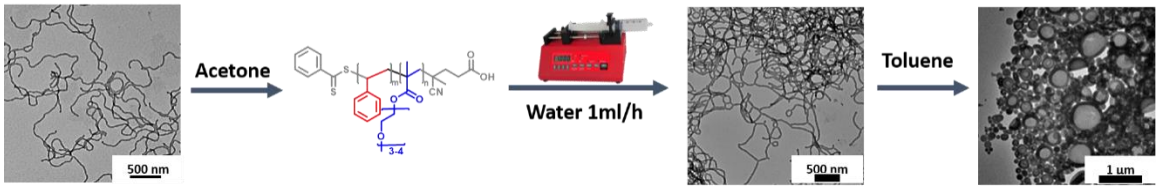


***Figure S14***: Formation of worms via traditional solution self-assembly of P(POEGMA-*b*-styrene) and the morphological transformation of worms to vesicles.

## References:

[1] F. L. Hatton, M. J. Derry, S. P. Armes, *Polym. Chem*. **2020**, *11*, 6343-6355.

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