# Mediating covalent crosslinking of single-chain nanoparticles through solvophobicity in organic solvents

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## S1. General Information

Reagents and solvents were purchased from commercial sources and used without further purification unless noted otherwise. 4-Cyanopentanoic acid dithiobenzoate (CPADB),[1] 2-(dodecylthiocarbonothioylthio)-2-methylpropionic acid ($Me_2C_{12}TTC$),[2] 7-(2-hydroxyethoxy)-4-methylcoumarin (CMOH),[3] 7-(2-methacryloyloxyethoxy)-4-methylcoumarin (CMA),[4] and 7-methoxy-4-methylcoumarin (CMOMe)[5] were synthesized according to previous reports. Dichloromethane (DCM), methanol (MeOH), and hexanes (Hx) were obtained from Fisher Scientific (ACS grade). Anhydrous *N,N*-dimethylformamide (DMF) and tetrahydrofuran (THF) were obtained by passing the solvent through two sequential activated alumina columns in a MBRAUN solvent purification system. All solvent mixtures are given in volume ratios. Thin-layer chromatography (TLC) was performed on $SiO_2$-60 $F_{254}$ aluminum plates with visualization by UV light or staining with $KMnO_4$. Flash column chromatography was performed using silica gel (40–60 µm particle size, 60 Å pore size) from VWR. UV light (4.0 mW/cm$^2$) was supplied from a UV nail gel-curing lamp (available online from ad hoc suppliers) with four 9 W bulbs and a peak emission near 365 nm (Figure S12).

## S2. Instrumentation

**Nuclear Magnetic Resonance (NMR) Spectroscopy.** 500 (125) MHz $^1H$ ($^{13}C$) NMR spectra were recorded on an INOVA 500 MHz spectrometer. Chemical shifts (δ) are given in parts per million (ppm) relative to TMS and referenced to residual protonated solvent purchased from Cambridge Isotope Laboratories, Inc. ($CDCl_3$: $\delta^1H$ 7.26 ppm, $\delta^{13}C$ 77.16 ppm).

**Size Exclusion Chromatography (SEC).** SEC of linear copolymers was performed in *N*,*N*-dimethylacetamide with 50 mM LiCl at 50 °C and a flow rate of 1.0 mL/min (Agilent isocratic pump, degasser, and autosampler; columns: Viscogel I-series 5 µm guard + two ViscoGel I-series G3078 mixed bed columns, molecular weight range 0−20 and 0−1000 kg/mol). Detection consisted of Wyatt Optilab T-rEX refractive index detector operating at 658 nm and a Wyatt miniDAWN TREOS light scattering detector operating at 690 nm. Absolute molecular weights and molecular weight distributions were calculated using the Wyatt ASTRA software and dn/dc values obtained from 100% mass recovery methods. In the 100% mass recovery methods, the polymer concentration was adjusted to account for small amounts of residual solvent, which was determined by thermogravimetric analysis.

SEC of SCNPs was conducted in THF, due to better solubility. The THF SEC system operated at 35 °C and a flow rate of 1.0 mL/min (Viscotek GPCmax pump, degasser, and autosampler; columns: three PLgel 5 µm MIXED-D mixed bed columns, molecular weight range 200−400000 g/mol). Detection consisted of a Wyatt Optilab rEX refractive index detector operating at 658 nm. Relative molecular weights were obtained through calibration with poly(styrene) (PS) standards of molecular weights ranging from 1.3 to 327 kg/mol.

**UV-Vis Spectroscopy**. UV-vis characterization was conducted on a Molecular Devices Spectra Max M2 spectrophotometer with quartz cuvettes with a 1 cm pathlength from Fisher Scientific.

**Static Light Scattering (SLS)**. SLS measurements were performed on an ALV/CGS-3 four-angle, compact goniometer system (Langen, Germany), which consisted of a 22 mW HeNe linear polarized laser operating at a wavelength of λ = 632.8 nm and scattering angles from θ = 42–150°. Radius of gyration ($R_g$), and molecular weight ($M_w$) were determined using the Zimm equation, which is a measure of the inverse scattering intensity as a function of the concentration of solution and scattering angle:

$$\frac{Kc}{R_\theta} = \frac{1}{M_w}\left(1 + \frac{q^2}{3}R_g\right) + 2Bc$$

where $K$ is the optical constant, $R_\theta$ is the Rayleigh ratio, $B$ is the second virial coefficient, and $c$ is the concentration of the polymer solution. A double extrapolation to zero concentration and zero angle will produce a y-intercept of $1/M_w$, while $B$ and $R_g$ can be extracted from the slopes of the zero-angle and zero-concentration extrapolation lines, respectively. All light scattering samples were performed at 25 °C, diluted to corresponding concentrations in 18 MΩ water, passed through a 0.45 µm PVDF syringe filter, and placed into a pre-cleaned borosilicate cuvette for analysis. The dn/dc values used in the analysis were determined with a Thermo Spectronic Refractometer at 25 ˚C from the slope of refractive index as a function of concentration for polymer solutions at six different concentrations.

## S3. Procedures

Typical RAFT copolymerization of methyl methacrylate (MMA) and CMA

CMA (0.481 g, 1.67 mmol), MMA (1.50 g, 15.0 mmol) and CPADB (0.019 g, 0.068 mmol) were dissolved in 4.2 mL of a mixture of DMF/dioxane (1/1, v/v) in a 10 mL Schlenk flask. AIBN was added (0.001 g, 0.007 mmol; from a stock solution in DMF) and the reaction mixture was purged with Ar for 20 min with stirring. The flask was placed in a preheated oil bath at 70 ˚C and reaction aliquots were withdrawn after regular time intervals and analyzed by $^{1}$H NMR and SEC. At the desired conversion, the reaction was quenched with air, and the polymer was precipitated into cold $Et_2O$ three times, followed by drying under vacuum.

**10 CMA-DTB:**

Final conversion (520 min): 60% MMA and 66% CMA

$M_n$ = 18300 g/mol; $Đ$ = 1.01

**20 CMA-DTB:**

Final conversion (510 min): 54% MMA and 62% CMA

$M_n$ = 20600 g/mol; $Đ$ = 1.01

General procedure for the methacrylate copolymer RAFT agent end-group removal

The polymer was dissolved in DMF (polymer concentration ~ 150 mg/mL) and thoroughly purged with Ar. Hydrazine monohydrate (5 molar equiv with respect to RAFT end-groups) dissolved in degassed DMF (hydrazine concentration ~ 0.2 M) was added to the reaction mixture. After 5 min of stirring, methyl acrylate (100 equiv.) was added, and the reaction was stirred overnight. The polymers were purified by precipitation into cold $Et_2O$ three times, followed by drying under vacuum.

**10 CMA:**

$M_n$ = 19300 g/mol; $Đ$ = 1.01 (Figures 2D and S3)

**20 CMA:**

$M_n$ = 20700 g/mol; $Đ$ = 1.02 (Figure S4)

*Typical SCNP-formation*

The copolymer (10 mg) was dissolved in DCM (50 mL). Methanol (50 mL) was added slowly under rapid stirring. The reaction mixture was purged with Ar for 15 min before being placed 2 cm from the UV light source ($\lambda_{max}$ = 365 nm) at an intensity of 4.0 mW/cm$^2$ (upon irradiation the reaction would heat up to about 35 ˚C). After 8.5 h, the conversion was determined by UV-vis spectroscopy (Figure S7) and the SCNPs were obtained after solvent evaporation (Table S2).

For experiments with kinetic monitoring, 20 mg of polymer in 200 mL total solvent were used. After regular time intervals, reaction aliquots (3 mL) were withdrawn and analyzed by UV-vis spectroscopy (Figure S8). The coumarin concentration was calculated from the absorbance value at 319 nm and the molar extinction coefficient in that respective solvent (Figures S8, S10, and Table S3)

Kinetic monitoring of the photodimerization of CMOMe

Since the concentration needed for efficient dimerization within a reasonable timescale for the molecular coumarin system was too high for UV-vis spectroscopy (beyond the linear regime), we turned to $^1$H NMR spectroscopy. CMOMe was weighed into a screwcap vial with 1,3,5-trimethoxybenzene as an internal standard and purged with Ar. Degassed solvent was added to adjust the CMOMe concentration to 0.15 M. The solution was irradiated with UV light ($\lambda_{max}$ = 365 nm; 4.0 mW/cm$^2$) and after solvent removal the coumarin conversion was determined via $^1$H NMR by comparing the coumarin proton resonances at 7.52, 6.88, 6.84, and 6.16 ppm with the internal standard peak at 6.11 ppm (Figure S13, Table S4). (In a preliminary experiment the photostability of 1,3,5-trimethoxybenzene was confirmed via $^1$H NMR.)

## S4. Supplementary Figures

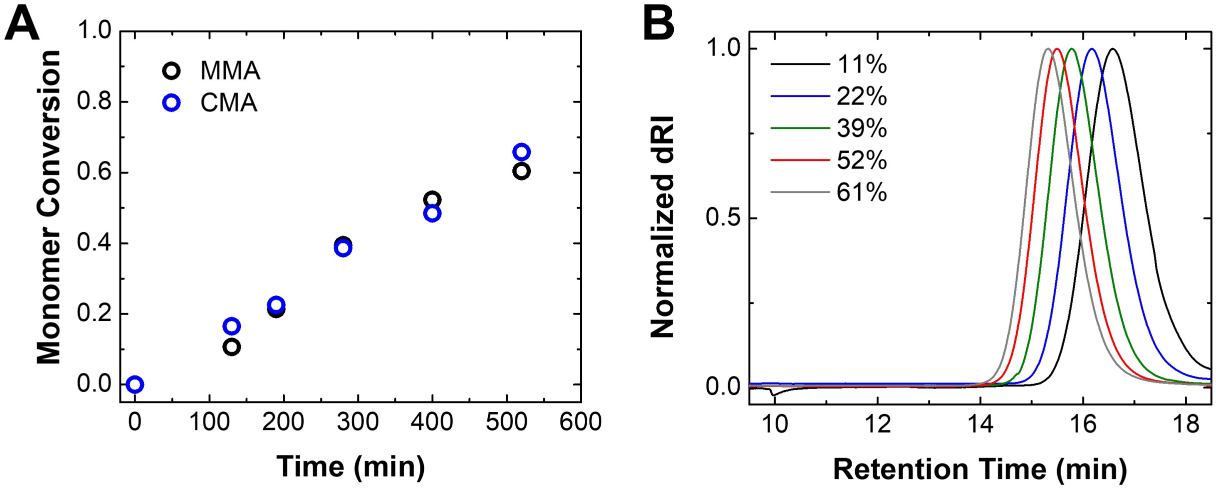


**Figure S1.** Characterization of the RAFT polymerization of 10 CMA-DTB. A) Monomer conversion plot obtained from $^1$H NMR spectroscopy and (B) SEC analysis in DMAc of reaction aliquots. The average monomer conversion for each SEC trace is indicated in the legend of the plot. The corresponding pseudo-first-order kinetic plot of this polymerization is shown in Figure 2.

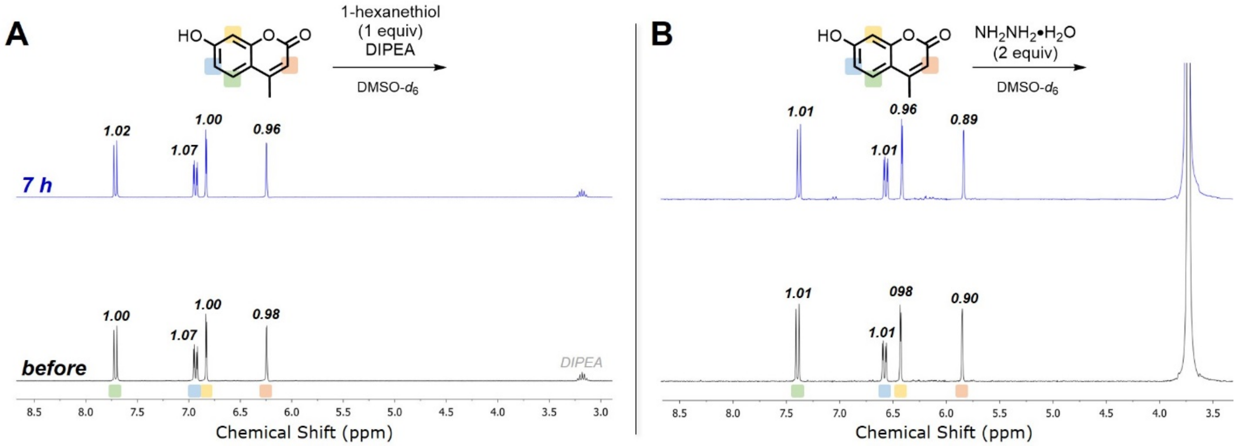


**Figure S2.** Stability study of 7-hydroxy-4-methylcoumarin via $^1$H NMR spectroscopy. The coumarin proton resonances were retained after 7 h incubation with (A) free thiols and (B) excess hydrazine.

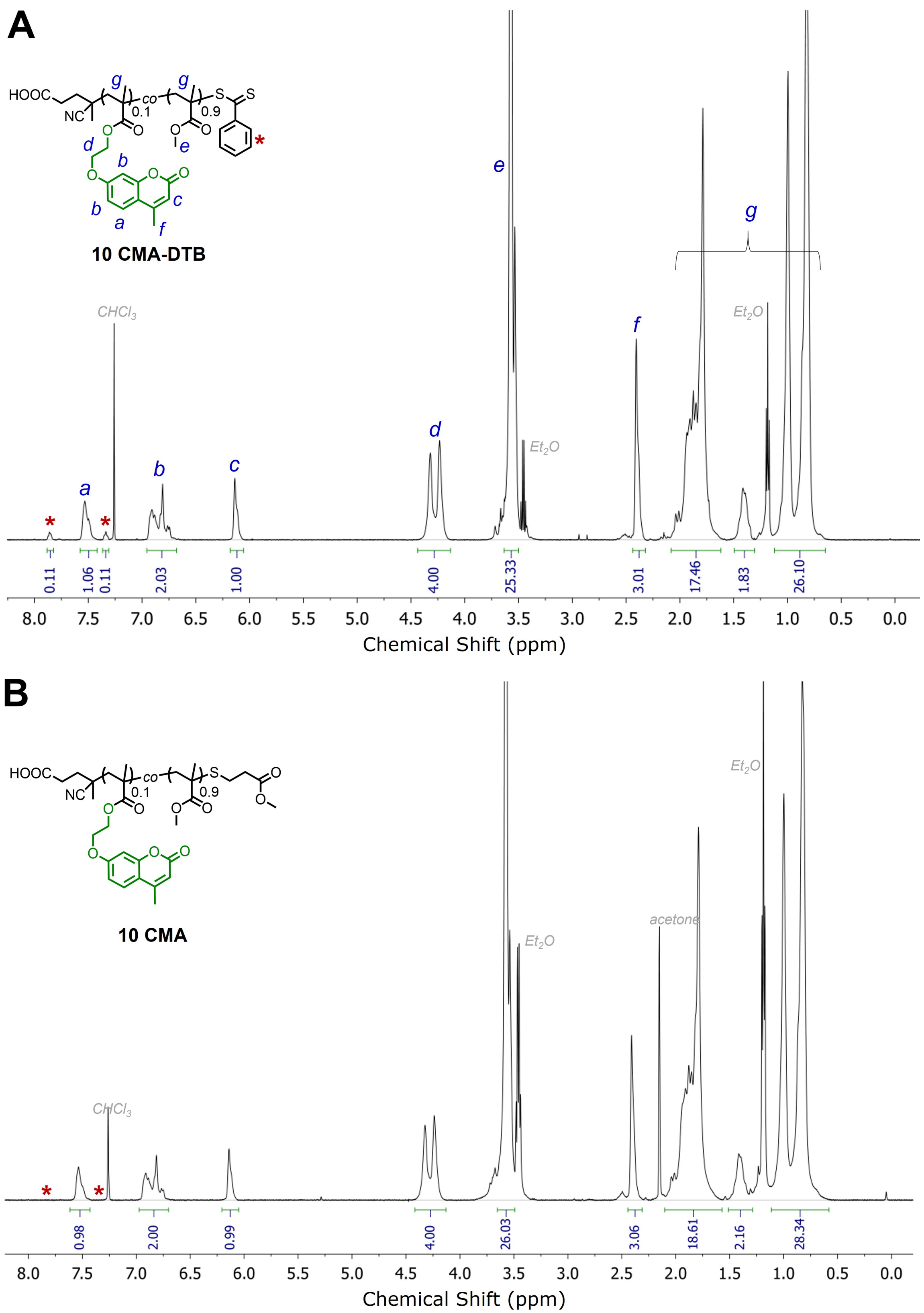


**Figure S3.** $^1$H NMR spectra in $CDCl_3$ of (A) 10 CMA-DTB and (B) 10 CMA after dithiobenzoate end-group removal.

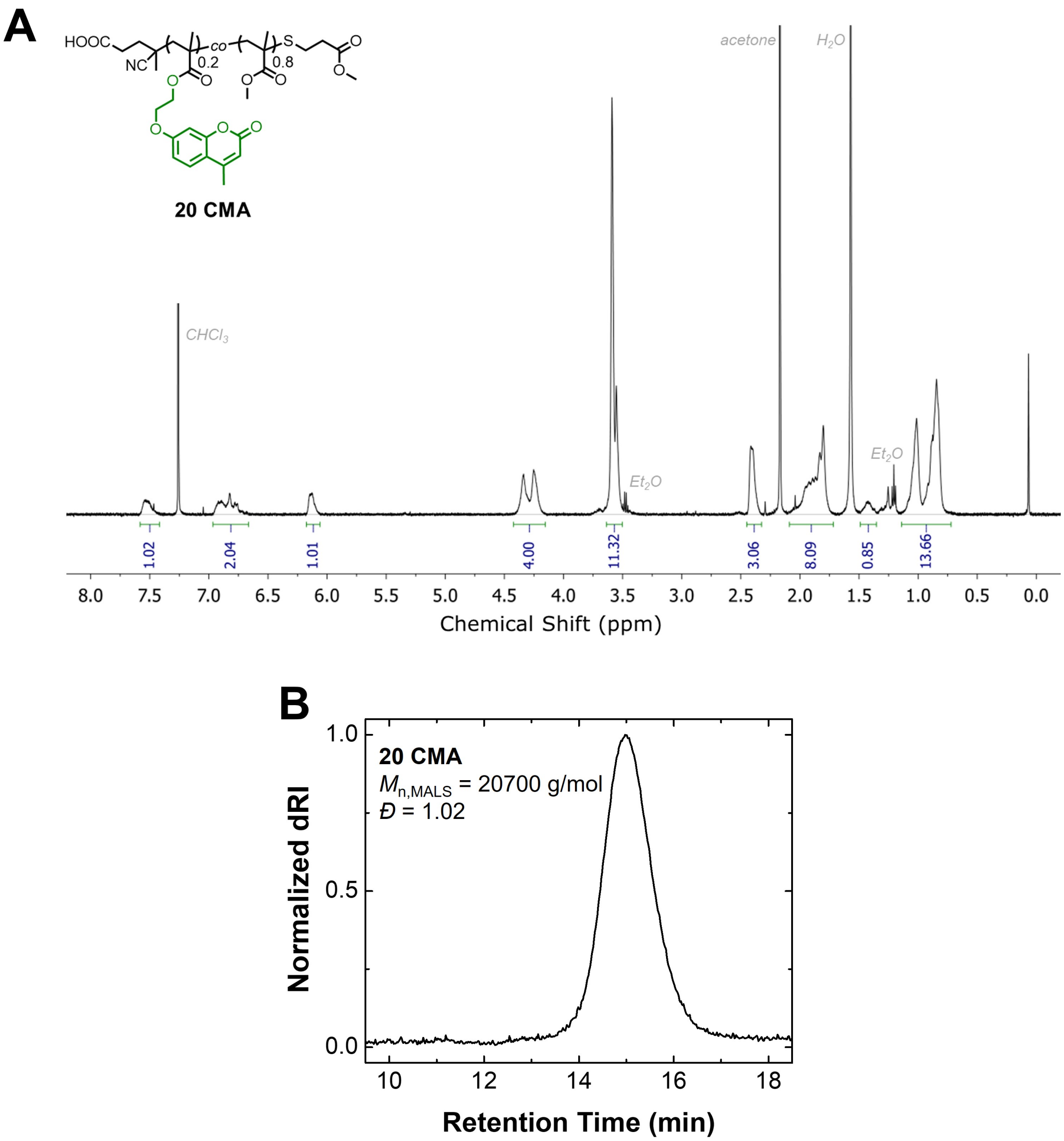
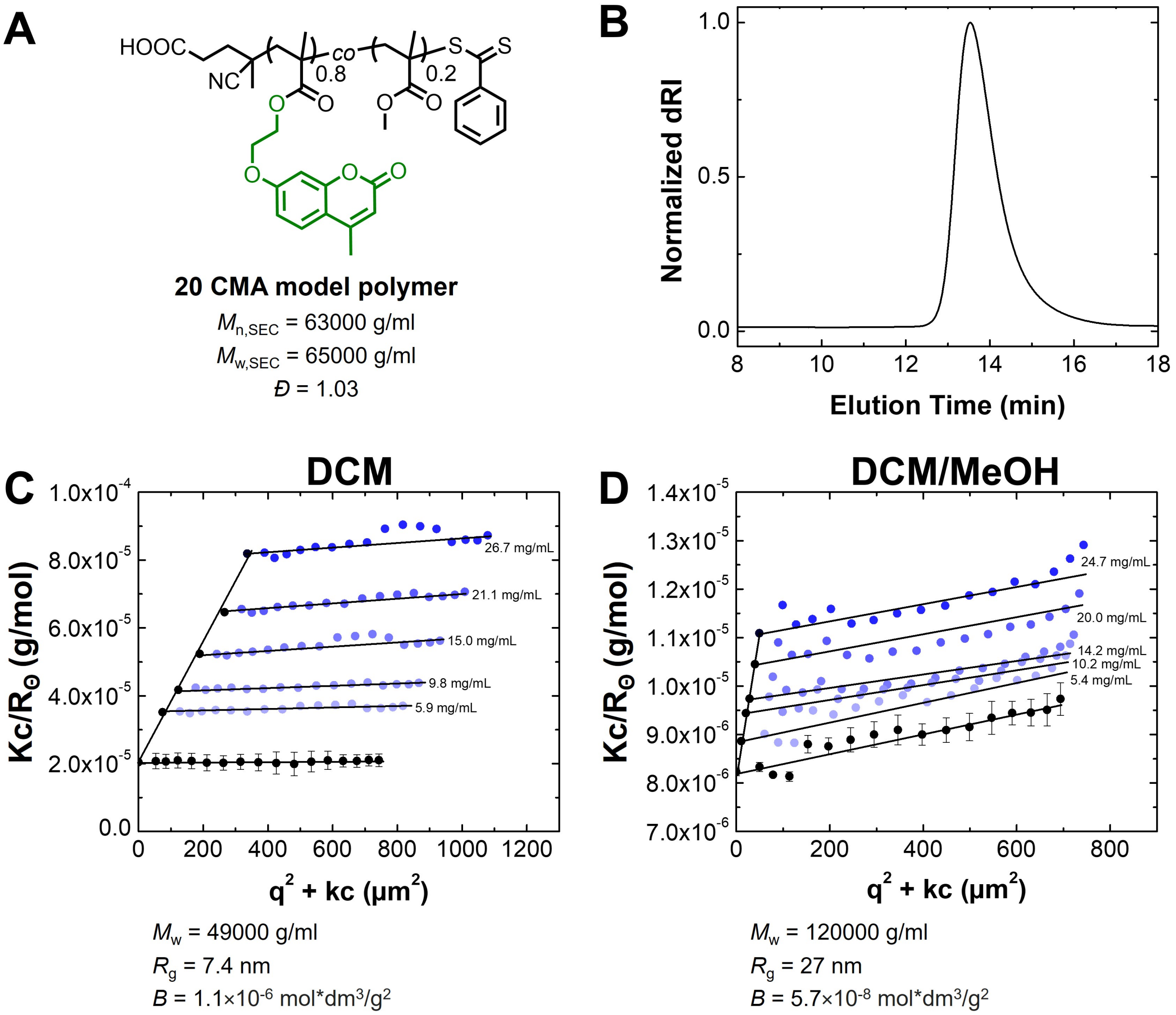


**Figure S4.** Characterization of 20 CMA. (A) $^1$H NMR spectrum in $CDCl_3$. (B) SEC analysis in DMAc. The number-average molecular weight ($M_n$) and dispersity ($Đ$) were obtained via multi-angle light scattering (MALS) detection.



**20 CMA model polymer**

$M_{n,SEC}$ = 63000 g/ml

$M_{w,SEC}$ = 65000 g/ml

$Đ$ = 1.03

(C)

$M_w$ = 49000 g/ml

$R_g$ = 7.4 nm

$B = 1.1\times10^{-6}$ mol*dm$^3$/g$^2$

(D)

$M_w$ = 120000 g/ml

$R_g$ = 27 nm

$B = 5.7\times10^{-8}$ mol*dm$^3$/g$^2$

**Figure S5.** Static light scattering (SLS) analysis of the 20 CMA model polymer to determine the second virial coefficient *B*. (A) Molecular weights and *Đ* obtained from (B) SEC coupled with MALS detection. Zimm plot of 20 CMA model polymer in (C) DCM and (D) DCM/MeOH, where k is a spreading factor to separate superposed data. The high molecular weight and larger $R_g$ in DCM/MeOH indicate aggregation of the polymer chains, likely due to the much higher molecular weight used in these SLS studies.

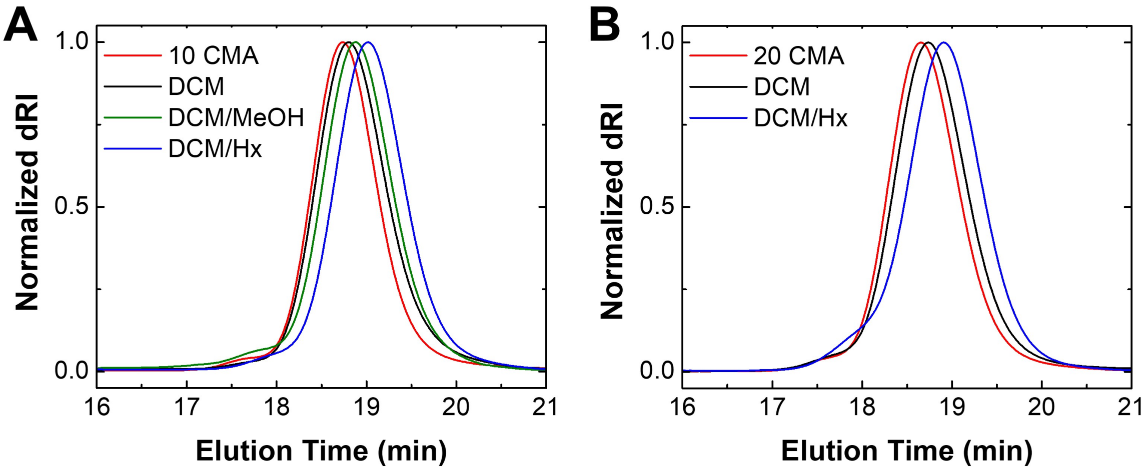


**Figure S6.** SEC analysis in THF of SCNPs formed under varying solvent conditions. (A) 10 CMA; coumarin conversions: 54% (DCM), 78% (DCM/MeOH), 66% (DCM/Hx). (B) 20 CMA: 57% (DCM), 57% (DCM/Hx). The comparison between the two 20 CMA SCNPs with 57% coumarin conversion shows that also for DCM vs. DCM/Hx at equal coumarin conversion, DCM/Hx afforded substantially more compacted SCNPs (see Table S2 for the compiled SCNP data).

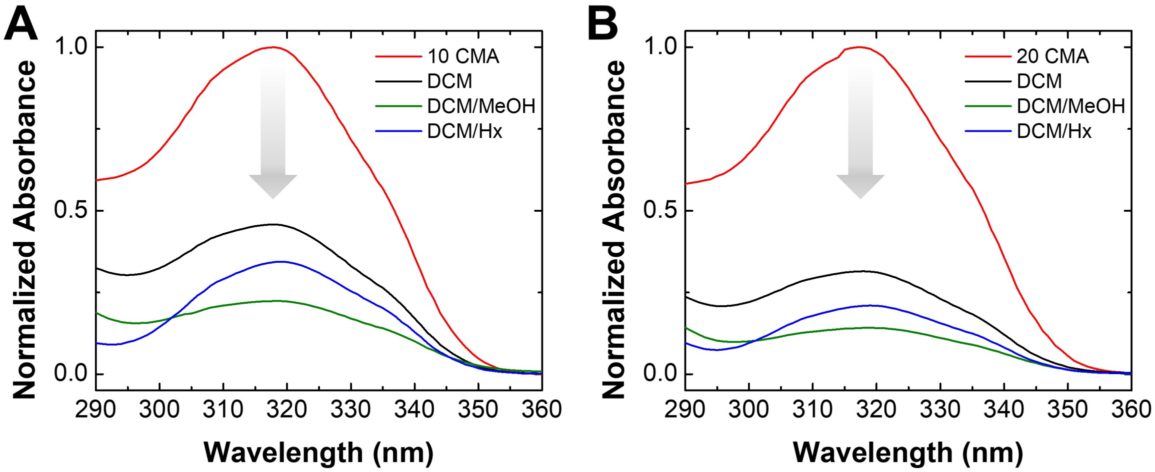


**Figure S7.** UV-vis spectra of linear precursors and SCNPs to determine the final coumarin conversion. (A) 10 CMA: 54% (DCM), 78% (DCM/MeOH), 66% (DCM/Hx). (B) 20 CMA: 69% (DCM), 86% (DCM/MeOH), 79% (DCM/Hx. See Table S2 for a compilation of UV-vis and SEC data.

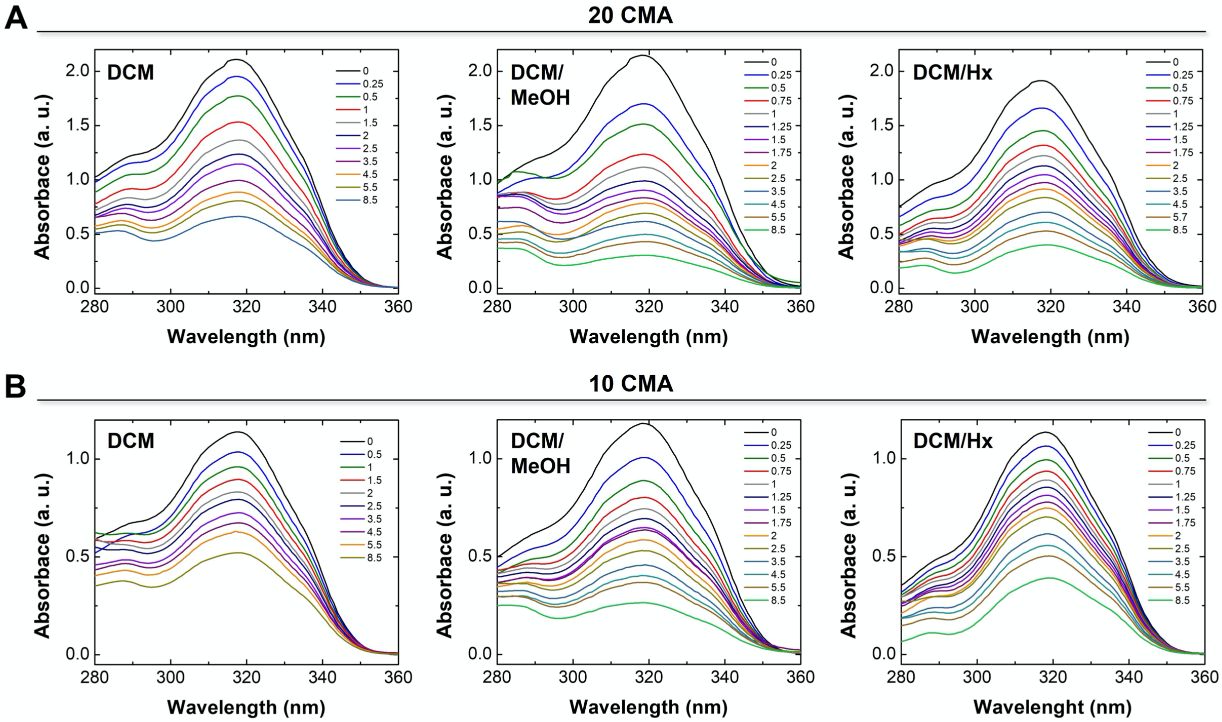


**Figure S8.** UV-vis spectra of reaction aliquots during the SCNP formation with 20 CMA (top) and 10 CMA (bottom). For a summary of absorbance and concentration data see Table S3.

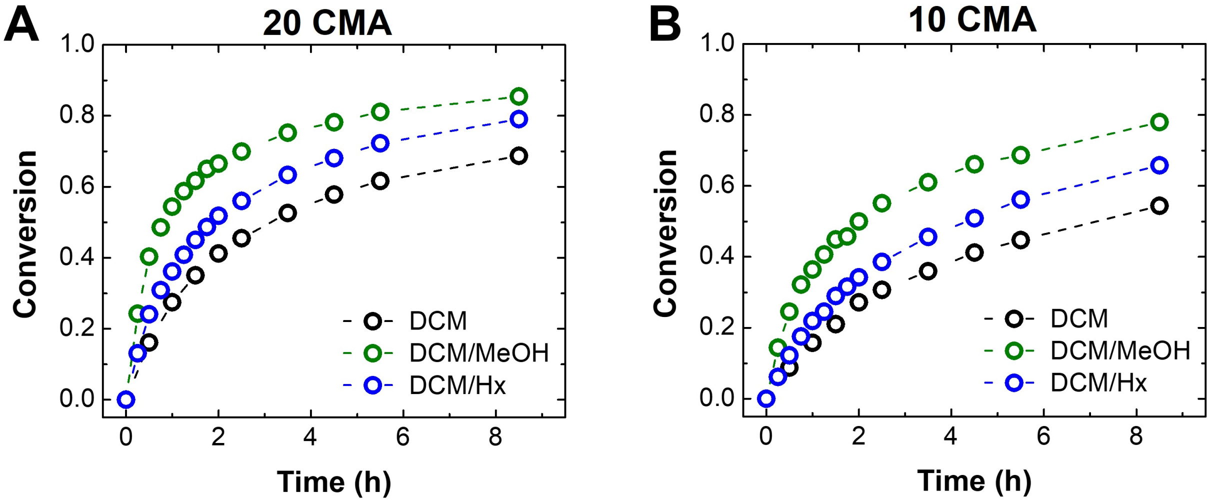
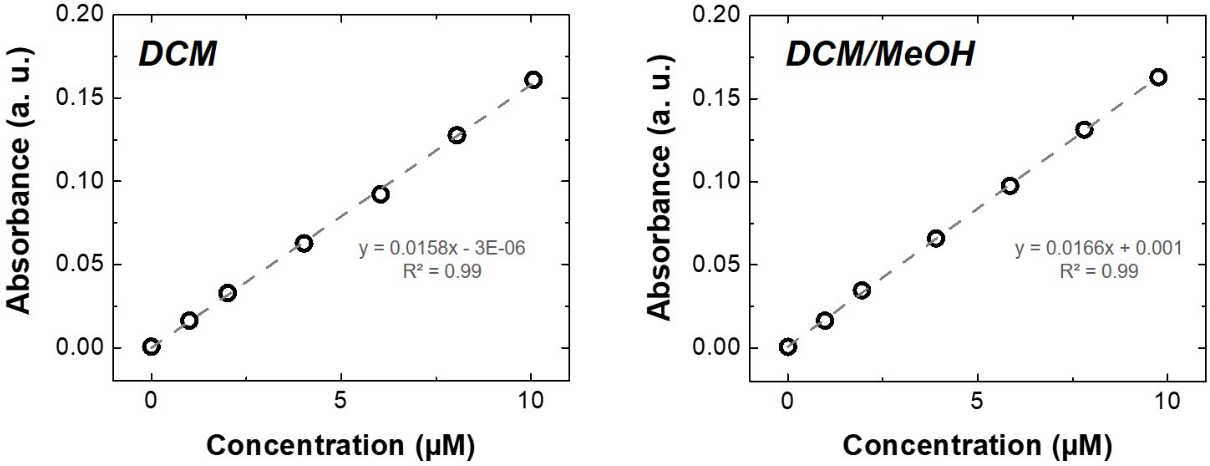
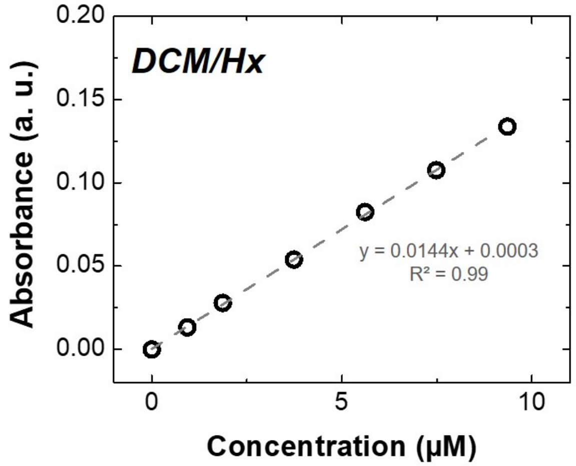
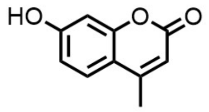


**Figure S9.** Conversion of coumarin units vs. time for (A) 20 CMA and (B) 10 CMA, determined from UV-vis spectroscopy.

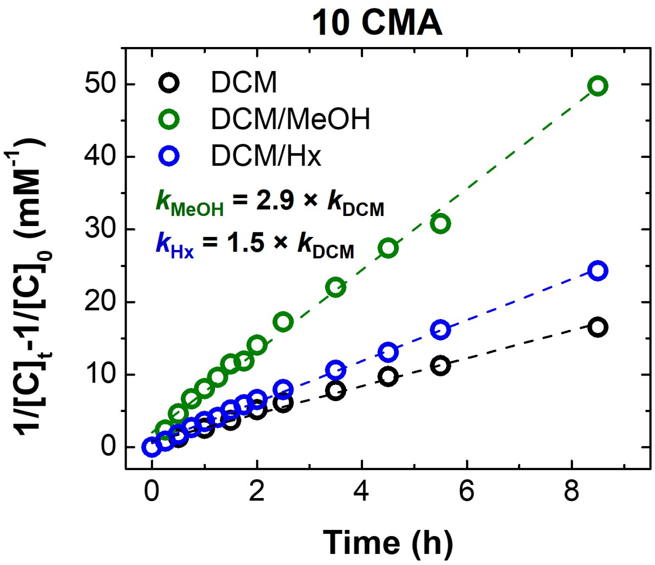






| Solvent | ε [$M^{-1}$*$cm^{-1}$] |
|---|---|
| DCM | 15800 |
| DCM/MeOH | 16600 |
| DCM/Hx | 14400 |

**Figure S10.** Determination of the molar extinction coefficient ($\varepsilon$) of a coumarin model compound (4-methylumbelliferone). We used $\varepsilon$ to obtain coumarin concentration directly from UV-vis absorbance in the kinetic experiments (Table S3).



$k_{MeOH}$ = 5.60 h*mM$^{-1}$  $k_{Hx}$ = 2.83 h*mM$^{-1}$  $k_{DCM}$ = 1.92 h*mM$^{-1}$

**Figure S11.** Second-order rate analysis for the photo-crosslinking of 10 CMA ($R^2$ equal or greater than 0.99 for all solvent conditions).

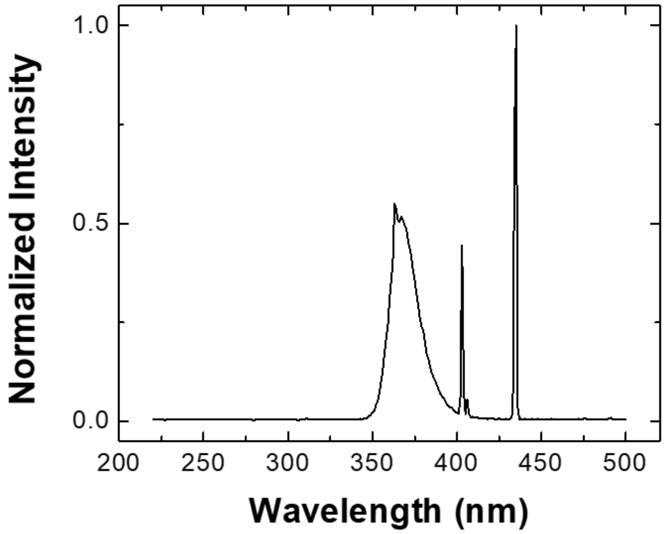


**Figure S 12.** Normalized emission spectrum of the UV light source (UV nail gel-curing lamp).

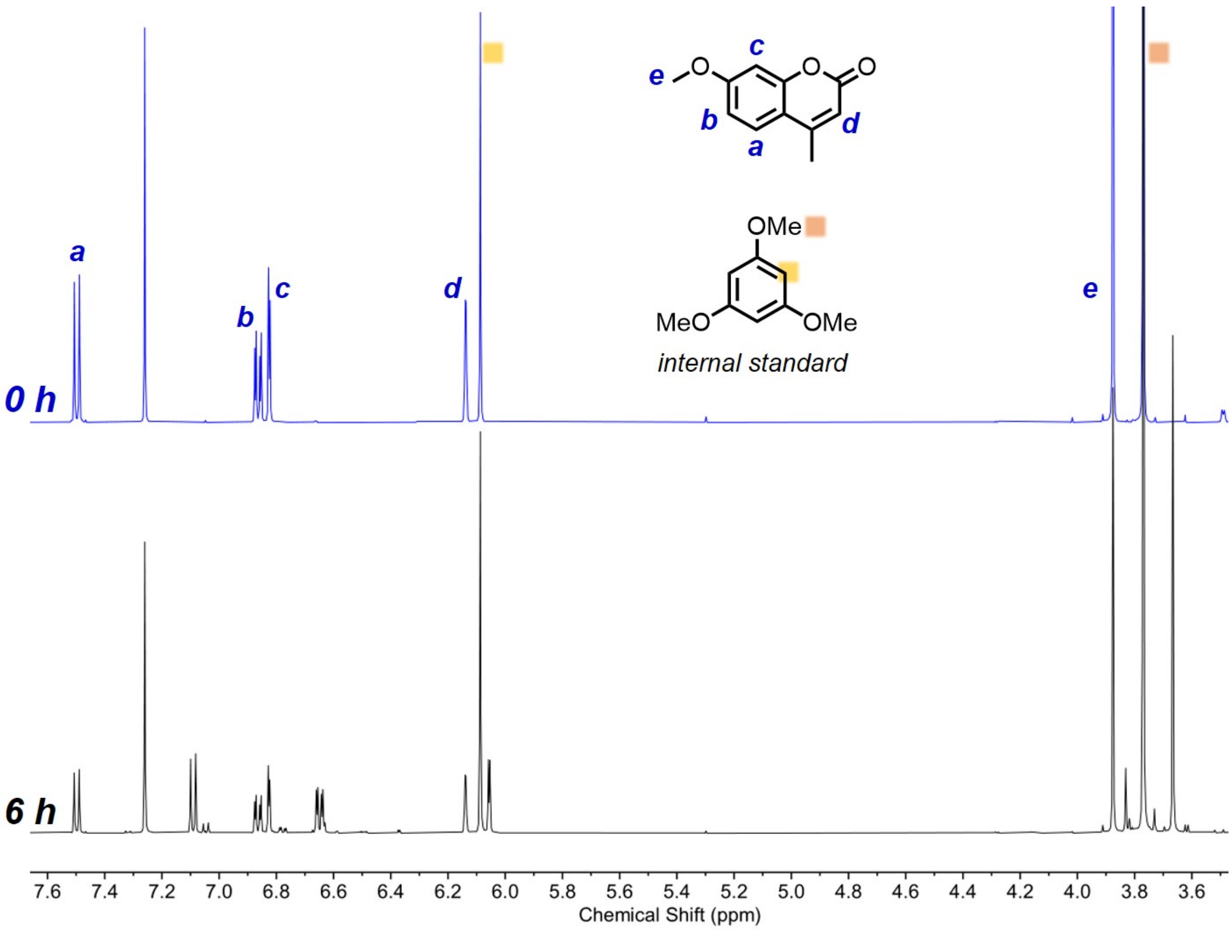


**Figure S13.** Representative $^1$H NMR spectra before (blue) and after (black) 6 h irradiation of a solution of CMOMe in DCM/MeOH. Conversion was determined by comparing the characteristic coumarin proton resonances at 7.52, 6.88, 6.84, and 6.16 ppm with the internal standard (1,3,5-trimethoxybenzene) peak at 6.11 ppm. See Table S4 for the compiled data of all $^1$H NMR experiments.

## S5. Supplementary Tables

**Table S1**. Parent polymers used for chain compactions and kinetic studies.

| Polymer | DP[a] | $M_{n,PS}$ (g/mol)[b] | $Đ$[b] | $M_{p,PS}$ (g/mol)[b] |
|---|---|---|---|---|
| **10 CMA** | 162 | 13300 | 1.07 | 14000 |
| **20 CMA** | 150 | 13500 | 1.08 | 14600 |

[a]Determined by $M_{n,MALS}$ in DMAc and the monomer ratio from $^1$H NMR spectroscopy. [b]Determined by SEC in THF and conventional calibration with PS standards.

**Table S2.** SCNPs formed from various parent polymers and under different solvent conditions. Coumarin conversions were determined from UV-vis spectroscopy after 8.5 h of irradiation at 365 nm, unless specified otherwise.

| Precursor | Solvent | $M_n$ (g/mol) | $Đ$ | $M_p$ (g/mol) | Coumarin conversion | $M_{p,SCNP}$ / $M_{p,PP}$ |
|---|---|---|---|---|---|---|
| **10 CMA** | DCM | 12300 | 1.08 | 13500 | 54% | 0.97 |
| | DCM/MeOH | 12100 | 1.12 | 12200 | 78% | 0.87 |
| | DCM/Hx | 11000 | 1.09 | 11700 | 66% | 0.84 |
| **20 CMA** | DCM | 11800 | 1.10 | 13500 | 69% | 0.93 |
| | DCM[a] | 12900 | 1.08 | 13800 | 57% | 0.95 |
| | DCM/MeOH | 11400 | 1.09 | 12000 | 86% | 0.82 |
| | DCM/Hx | 9300 | 1.14 | 10800 | 79% | 0.74 |
| | DCM/Hx[b] | 11700 | 1.12 | 12200 | 57% | 0.84 |

Molecular weight and dispersity ($Đ$) determined from SEC in THF and conventional calibration with PS standards. [a]5.5 h of irradiation. [b]3 h of irradiation. The comparison between the two 20 CMA SCNPs with 57% coumarin conversion shows that also for DCM vs. DCM/Hx at equal coumarin conversion, DCM/Hx afforded substantially more compacted SCNPs.

**Table S3.** Monitoring of coumarin dimerization kinetics through UV-vis spectroscopy during SCNP formation and second-order rate analysis. Coumarin concentration was determined using the molar extinction coefficient from a coumarin model compound (4-methylumbelliferone, Figure S10) in the respective solvent and the absorbance at 319 nm.

| Precursor | Solvent | Time (h) | Absorbance (a.u.) | Coumarin Conc. (mM) | $1/[C]_t - 1/[C]_0$ (mM$^{-1}$) |
|---|---|---|---|---|---|
| **20 CMA** | DCM | 0 | 2.11 | 0.134 | 0.00 |
| | | 0.5 | 1.77 | 0.112 | 1.44 |
| | | 1 | 1.53 | 0.097 | 2.84 |
| | | 1.5 | 1.37 | 0.087 | 4.04 |
| | | 2 | 1.24 | 0.078 | 5.25 |
| | | 2.5 | 1.15 | 0.073 | 6.25 |
| | | 3.5 | 1.00 | 0.063 | 8.31 |

| | | | | | |
|---|---|---|---|---|---|
| | | 4.5 | 0.89 | 0.056 | 10.3 |
| | | 5.5 | 0.81 | 0.051 | 12.0 |
| | | 8.5 | 0.66 | 0.042 | 16.5 |
| **20 CMA** | DCM/MeOH | 0 | 2.15 | 0.130 | 0.00 |
| | | 0.25 | 1.70 | 0.102 | 2.04 |
| | | 0.5 | 1.51 | 0.091 | 3.27 |
| | | 0.75 | 1.24 | 0.075 | 5.67 |
| | | 1 | 1.12 | 0.067 | 7.10 |
| | | 1.25 | 0.99 | 0.060 | 9.05 |
| | | 1.5 | 0.90 | 0.054 | 10.7 |
| | | 1.75 | 0.84 | 0.051 | 12.0 |
| | | 2 | 0.79 | 0.048 | 13.3 |
| | | 2.5 | 0.69 | 0.042 | 16.3 |
| | | 3.5 | 0.62 | 0.037 | 19.1 |
| | | 4.5 | 0.5 | 0.030 | 25.5 |
| | | 5.5 | 0.43 | 0.026 | 30.9 |
| | | 8.5 | 0.30 | 0.018 | 47.6 |
| **20 CMA** | DCM/Hx | 0 | 1.91 | 0.133 | 0.00 |
| | | 0.25 | 1.66 | 0.115 | 1.14 |
| | | 0.5 | 1.45 | 0.101 | 2.39 |
| | | 0.75 | 1.32 | 0.092 | 3.37 |
| | | 1 | 1.22 | 0.085 | 4.26 |
| | | 1.25 | 1.13 | 0.078 | 5.20 |
| | | 1.5 | 1.05 | 0.073 | 6.18 |
| | | 1.75 | 0.98 | 0.068 | 7.15 |
| | | 2 | 0.92 | 0.064 | 8.11 |
| | | 2.5 | 0.84 | 0.058 | 9.60 |
| | | 3.5 | 0.70 | 0.049 | 13.0 |
| | | 4.5 | 0.61 | 0.042 | 16.1 |
| | | 5.5 | 0.53 | 0.037 | 19.6 |
| | | 8.5 | 0.40 | 0.028 | 28.5 |
| **10 CMA** | DCM | 0 | 1.14 | 0.072 | 0.00 |
| | | 0.5 | 1.04 | 0.066 | 1.33 |
| | | 1 | 0.96 | 0.061 | 2.60 |
| | | 1.5 | 0.90 | 0.057 | 3.70 |
| | | 2 | 0.83 | 0.053 | 5.18 |
| | | 2.5 | 0.79 | 0.050 | 6.14 |
| | | 3.5 | 0.73 | 0.046 | 7.78 |
| | | 4.5 | 0.67 | 0.042 | 9.72 |
| | | 5.5 | 0.63 | 0.040 | 11.2 |
| | | 8.5 | 0.52 | 0.033 | 16.5 |
| **10 CMA** | DCM/MeOH | 0 | 1.18 | 0.071 | 0.00 |
| | | 0.25 | 1.01 | 0.061 | 2.37 |

| | | | | | |
|---|---|---|---|---|---|
| | | 0.5 | 0.89 | 0.054 | 4.58 |
| | | 0.75 | 0.80 | 0.048 | 6.68 |
| | | 1 | 0.75 | 0.045 | 8.07 |
| | | 1.25 | 0.70 | 0.042 | 9.65 |
| | | 1.5 | 0.65 | 0.039 | 11.5 |
| | | 1.75 | 0.64 | 0.039 | 11.9 |
| | | 2 | 0.59 | 0.036 | 14.1 |
| | | 2.5 | 0.53 | 0.032 | 17.3 |
| | | 3.5 | 0.46 | 0.028 | 22.0 |
| | | 4.5 | 0.40 | 0.024 | 27.4 |
| | | 5.5 | 0.37 | 0.022 | 30.8 |
| | | 8.5 | 0.26 | 0.016 | 49.8 |
| **10 CMA** | DCM/Hx | 0 | 1.14 | 0.079 | 0.00 |
| | | 0.25 | 1.07 | 0.074 | 0.83 |
| | | 0.5 | 1.00 | 0.069 | 1.77 |
| | | 0.75 | 0.94 | 0.065 | 2.69 |
| | | 1 | 0.89 | 0.062 | 3.55 |
| | | 1.25 | 0.86 | 0.060 | 4.11 |
| | | 1.5 | 0.81 | 0.056 | 5.15 |
| | | 1.75 | 0.78 | 0.054 | 5.83 |
| | | 2 | 0.75 | 0.052 | 6.57 |
| | | 2.5 | 0.70 | 0.049 | 7.94 |
| | | 3.5 | 0.62 | 0.043 | 10.6 |
| | | 4.5 | 0.56 | 0.039 | 13.1 |
| | | 5.5 | 0.50 | 0.035 | 16.2 |
| | | 8.5 | 0.39 | 0.027 | 24.3 |

**Table S4.** Monitoring of coumarin dimerization kinetics of CMOMe through $^1$H NMR spectroscopy and second-order rate analysis. Coumarin concentration was determined from conversion and the initial concentration of CMOMe (0.15 M).

| **Compound** | **Solvent** | **Time (h)** | **Conversion** | **Coumarin Conc. (M)** | **$1/[C]_t – 1/[C]_0$ (M$^{-1}$)** |
|---|---|---|---|---|---|
| **CMOMe** | DCM | 0 | 0.000 | 0.150 | 0.00 |
| | | 1 | 0.094 | 0.136 | 0.69 |
| | | 2 | 0.169 | 0.125 | 1.36 |
| | | 3 | 0.220 | 0.117 | 1.88 |
| | | 4 | 0.227 | 0.116 | 1.96 |
| | | 5 | 0.310 | 0.104 | 3.00 |
| | | 6 | 0.362 | 0.096 | 3.78 |
| **CMOMe** | DCM/MeOH | 0 | 0.000 | 0.150 | 0.00 |
| | | 1 | 0.169 | 0.125 | 1.36 |
| | | 2 | 0.277 | 0.108 | 2.55 |

| | | | | | |
|---|---|---|---|---|---|
| | | 3 | 0.383 | 0.093 | 4.14 |
| | | 4 | 0.421 | 0.087 | 4.85 |
| | | 5 | 0.474 | 0.079 | 6.01 |
| | | 6 | 0.551 | 0.067 | 8.18 |
| **CMOMe** | DCM/Hx | 0 | 0.000 | 0.150 | 0.00 |
| | | 1 | 0.098 | 0.135 | 0.72 |
| | | 2 | 0.172 | 0.124 | 1.38 |
| | | 3 | 0.222 | 0.117 | 1.90 |
| | | 4 | 0.269 | 0.110 | 2.45 |
| | | 5 | 0.322 | 0.102 | 3.17 |
| | | 6 | 0.361 | 0.096 | 3.77 |

**Table S5**. Coumarin dimerization rate constants determined from the slope of the second-order rate plots for 10 CMA (Figure S11), 20 CMA, and CMOMe (both in Figure 4) in different solvents.

| **Sample** | $k_{\mathrm{DCM}}$ | $R^2_{\mathrm{DCM}}$ | $k_{\mathrm{Hx}}$ | $R^2_{\mathrm{Hx}}$ | $k_{\mathrm{MeOH}}$ | $R^2_{\mathrm{MeOH}}$ |
|---|---|---|---|---|---|---|
| **10 CMA** | 1.92 h*mM$^{-1}$ | 0.99 | 2.83 h*mM$^{-1}$ | 0.99 | 5.60 h*mM$^{-1}$ | 0.99 |
| **20 CMA** | 1.93 h*mM$^{-1}$ | 0.98 | 3.34 h*mM$^{-1}$ | 0.99 | 5.43 h*mM$^{-1}$ | 0.99 |
| **CMOMe** | 0.59 h*M$^{-1}$ | 0.97 | 0.62 h*M$^{-1}$ | 0.99 | 1.29 h*M$^{-1}$ | 0.99 |

## S6. References

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