A triple carboxylic acid-functionalized RAFT agent platform for the elaboration of well-defined telechelic 3-arm star PDMAc

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Materials

1,3,5-Tris(bromomethyl)benzene (97%), 3-Mercaptopropionic acid (≥ 99%), Carbon disulfide (anhydrous, ≥ 99%), Diisopropyl azodicarboxylate (DIAD, 98%), Triphenylphosphine (≥ 98.5), 1,1'-Azobis(cyclohexanecarbonitrile) (V-40, 98%), Potassium phosphate tribasic (K_3PO_4, ≥ 98%), Benzene (99.9%), 1,3,5-Trioxane (≥ 99%), $[(CH_3CN)_4Cu]PF_6$ (97%), tetraethylammonium chloride (≥ 98%) and ammonium hexafluorophosphate (≥ 98%) were purchased from Sigma Aldrich and were used as received. *N,N*-Dimethylacrylamide (DMAc, 99%) were purified by vacuum distillation under reduced pressure at room temperature before use. All polymerizations were conducted under argon atmosphere. 1-[2-(2-Hydroxyethoxy)ethoxy]-5-[2-(2-methoxyethoxy)ethoxy]naphthalene **2**,[i] the tetracationic cyclophane cyclobis(paraquat-*p*-phenylene)-alkyne (HC≡C-CBPQT^{4+}, 4PF$_6^-$) **4**,[ii] 1,6-diazidohexane **5**[iii] and CBPQT^{4+}, 4Cl$^-$ **7**[iv] were synthesized according to literature procedures.

Instrumentation

Nuclear Magnetic Resonance (NMR). The purity of RAFT agents, homoditopic tetracationic macrocycle cyclobis(paraquat-*p*-phenylene) **6** and star polymers was determined by ^{1}H and ^{13}C NMR spectroscopy in acetone-d_6, CDCl$_3$ or D$_2$O at room temperature (Bruker Advance 200 or 500 MHz spectrometer). The conversion of DMAc was determined by ^{1}H NMR spectroscopy in acetone-d_6 by the relative integration of the internal reference (1,3,5-trioxane) peak at 5.1 ppm and the vinylic proton peaks of DMAc at 6.6, 6.3 and 5.7 ppm.

Isothermal titration calorimetry (ITC) experiments were performed at 20 °C using a MicroCal VP-ITC titration calorimeter from Malvern with a sample cell volume of 1.42 mL. A 300 µL injection syringe was used with stirring at 260 rpm. Host molecules were dissolved in water and the solutions were

degassed gently under vacuum before use. Each titration comprised an initial 5 μL preinjection followed by 60 × 5 μL injections of **CBPQT^{4+}, 4Cl$^-$** (7.3 mM) into guest (**P$_2$**) solution (0.30 mM). Control experiments with identical injections of **CBPQT^{4+}, 4Cl$^-$** into water alone were used to correct titration data.

Size exclusion chromatography (SEC). The number-average molar masses (M_n), the weight-average molar masses (M_w), and the dispersities ($Đ = M_w/M_n$) were determined by SEC. Measurements were performed in DMF (+ LiBr, 1g L^{-1}) at 60 °C, at a flow rate of 0.8 mL min^{-1} and at a polymer concentration of 5 mg mL^{-1} after filtration through a 0.22 μm pore-size membrane. The chromatography was carried out on two PSS GRAM 1000 Å columns (8 × 300 mm; separation limits: 1 to 1000 kg mol^{-1}) and one PSS GRAM 30 Å (8 × 300 mm; separation limits: 0.1 to 10 kg mol^{-1}) coupled with three detectors (Viscotek, TDA 305): a differential refractive index (RI) detector, a viscosimeter detector and a light scattering (LS) detector (laser λ = 670 nm at 7° and 90°). The number-average molar masses, M_n^{PMMA}, and the dispersities ($Đ = M_w/ M_n$), were calculated with a calibration curve based on narrow poly(methyl methacrylate) (PMMA) standards (from Polymer Standard Services), using only the RI detector. The absolute number-average molar masses, M_n^{LS}, were calculated using the RALS/LALS and RI signals. In all plots showing the evolution of M_n with monomer conversion, the straight line corresponds to the expected evolution of the theoretical number-average molar mass, M_n^{th}, calculated by the product of the introduced mass of monomer and the conversion divided by the initial mole number of the RAFT agent plus the molar mass of the latter.

Matrix-assisted laser desorption and ionization time-of-flight (MALDI-TOF) mass spectrometry. Mass spectra were recorded by MALDI-TOF mass spectrometry using a Bruker autoflex III smartbeam mass spectrometer, equipped with the laser that produces pulses at 337 nm using dithranol as a matrix and NaI as cationizing agent. Spectra were recorded in linear mode at an accelerating potential of 20 kV. Samples were prepared by dissolving the RAFT agent in THF at a concentration of 3 mg mL^{-1}. A 10 μL aliquot of this solution was mixed with 20 μL of matrix solution and 10 μL of NaI solution (both at 20 mg mL^{-1} in THF). Standard (polystyrene of known structure, M_n = 1.2 kg mol^{-1} purchased from Polymer Standards Service) was used to calibrate the mass scale. In all cases, to determine m/z, the molar mass of the sodium cation was added.

Preparation of the chain transfer agents: 1 and 3

Synthesis of the tri(carboxylic acid)-functionalized RAFT agent (1): 1,3,5-Tris((3-propionic acid)sulfanylthiocarbonyl-sulfanylmethyl)benzene

3-mercaptopropionic acid (3.35 g, 32 mmol) was added to 50 mL round-bottomed flask equipped with a magnetic stir bar containing a mixture of K_3PO_4 (6.74 g, 32 mmol) in 15 mL of acetone. This mixture was stirred for 5 min prior to the dropwise addition of carbon disulfide (4.41 g, 58 mmol). The resulting yellow solution was stirred 10 min. A solution of 1,3,5-tris(bromomethyl)benzène (2.11 g, 6.3 mmol) in 5 mL was added dropwise to the solution and the mixture was stirred 2h at room temperature. The mixture was filtered and the precipitate was dissolved in 500 mL of deionized water. The mixture was acidified by the addition of concentrated hydrochloric acid and the resulting precipitate was collected using a Bucher funnel and flask. The product was washed with deionized water and then dried in vacuum overnight to obtain **1** (2.62 g, 63%) as a yellow powder.

^{1}H NMR (200 MHz, $(CD_3)_2CO$), δ (ppm from TMS): 7.38 (s, 3H, **H_a**), 4.67 (s, 6H, **H_b**), 3.64 (t, J= 6.9 Hz, 6H, **H_c**), 2.79 (t, J= 6.9 Hz, 6H, **H_d**).

^{13}C NMR (200 MHz, $(CD_3)_2CO$), δ (ppm from TMS): 32.5 (CH_2-**C**H_2-COOH), 33.0 (S-**C**H_2-CH_2), 41.0 (Ph-**C**H_2-S), 130.4 (ar-**C**-H), 137.6 (ar-**C**-CH_2), 172.7 (**C**OO), 224.3 (-**C**=S).

FT-IR (cm^{-1}, ATR): 3000 (O-H), 1711 (C=O), 1066 (C=S), 811 (C_{Ar}-H).

Maldi-Tof MS: (m/z): $[M+Na]^+$ calcd. for $C_{21}H_{24}NaO_6S_9$, 683.95; found, 683.72 (see Fig. S18).
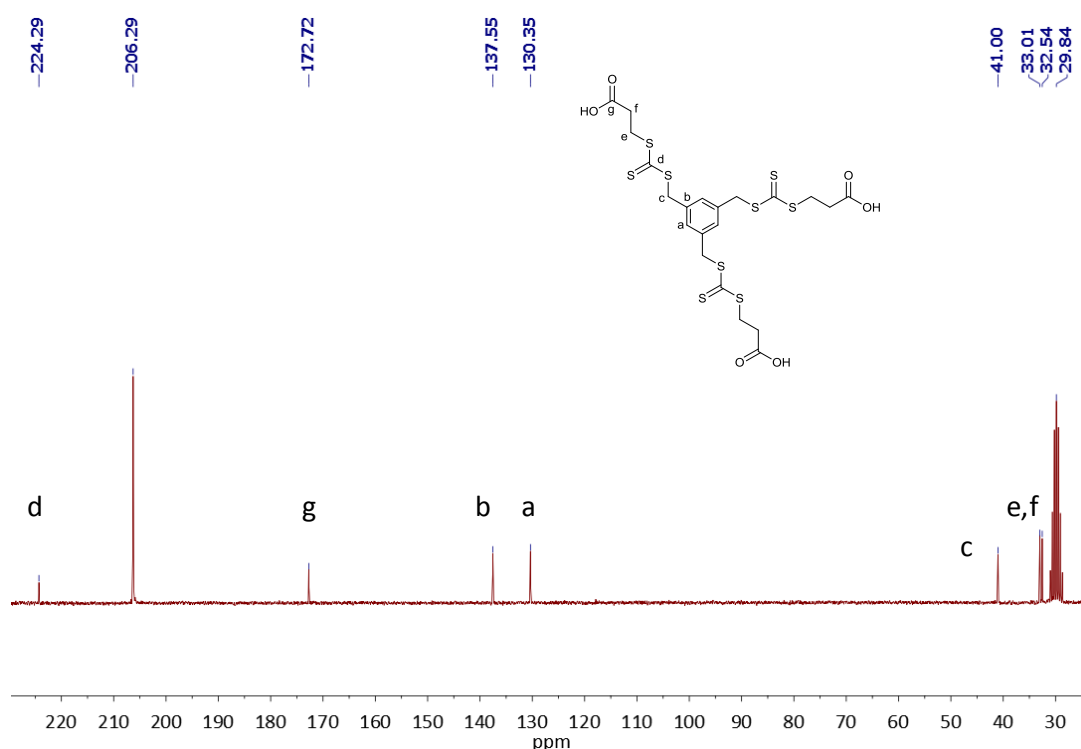

Fig. S1 ^{13}C NMR spectrum of the tri(carboxylic acid)-functionalized RAFT agent **1** recorded in acetone_d_6 at 25°C.

Synthesis of the tri(dialkyloxynaphthalene)-functionalized RAFT agent (3): 1,3,5-Tris((3-(1-[2-(2-Hydroxyethoxy)ethoxy]-5-[2-(2-methoxyethoxy)ethoxy]naphthalene) propionate) Sulfanylthiocarbonylsulfanylmethyl)benzene

1,3,5-Tris((3-propionic acid)sulfanylthiocarbonyl-sulfanylmethyl)benzene **1** (0.27 g, 0.41 mmol), 1-[2-(2-Hydroxyethoxy)ethoxy]-5-[2-(2-methoxyethoxy)ethoxy]naphthalene **2** (0.45 g, 1.28 mmol) and triphenylphosphine (0.33 g, 1.25 mmol) were added to a 25 mL round-bottomed flask equipped with a magnetic stir bar and a Rotaflo® stopcock and dried under vacuum at room temperature for 3.5 h. 9 mL of anhydrous tetrahydrofuran were injected with a purged syringe. The resulting mixture was cooled with a cold water bath under argon atmosphere and stirred for 5 min prior to the dropwise addition of DIAD (0.31 g, 1.52 mmol). This mixture was stirred overnight at room temperature. The solvent was evaporated to afford a crude product which was subjected to column chromatography (SiO$_2$: ethyl acetate / petroleum spirit, 8:2 (first column) and acetone (second column)). The fractions containing the product were combined and the eluent was removed in vacuum, affording the product as dark yellow oil **3** (0.30 g, yield = 44 %, R$_f$ = 0.83).

^{1}H NMR (200 MHz, CDCl$_3$), δ (ppm from TMS): 7.85 (m, 6H, **H$_k$**), 7.34 (ddd, *J* = 8.7, 7.6, 1.2 Hz, 6H, **H$_j$**), 7.15 (s, 3H, **H$_a$**), 6.83 (dt, *J* = 7.7, 1.0 Hz, 6H, **H$_i$**), 4.50 (s, 6H, **H$_b$**), 4.29 (m, 18H, **H$_e$** and **H$_h$**), 4.00 (m, 12H, **H$_g$**), 3.81 (m, 12H, **H$_f$**), 3.58 (m, 12H, **H$_c$** and **H$_l$**), 3.40 (s, 9H, **H$_m$**), 2.77 (t, *J* = 6.9 Hz, 6H, **H$_d$**).

^{13}C NMR (200 MHz, CDCl$_3$), δ (ppm from TMS): 31.6 (**C**H$_2$-COO-), 33.1 (S-**C**H$_2$-CH$_2$), 40.9 (Ph-**C**H$_2$-S), 59.2 (**C$_r$**), 64.2 (**C$_h$**), 59.2-72.2 (**C$_{i, j, k, q}$**), 105.9 (**C$_m$**), 114.8 (**C$_o$**), 125.2 (**C$_n$**), 126.9 (**C$_p$**), 129.6 (ar-**C**-H), 136.3 (ar-**C**-CH$_2$), 154.4 (**C$_l$**), 171.5 (**C**OO), 222.5 (-**C**=S).

FT-IR (cm^{-1}, ATR): 2925, 2876 (C-H), 1735 (C=O), 1508 (C=C), 1079 (C-O), 1069 (C=S), 775 (C$_{Ar}$-H).

Maldi-Tof MS: (m/z): [M+Na]$^+$ calcd. for C$_{78}$H$_{96}$NaO$_{21}$S$_9$, 1681.13; found, 1680.81 (see Fig. S18).
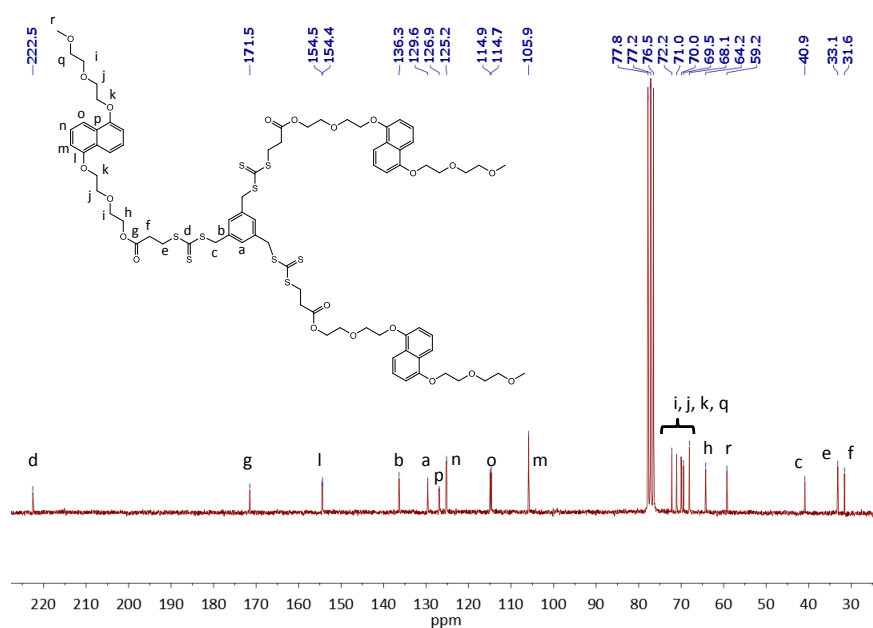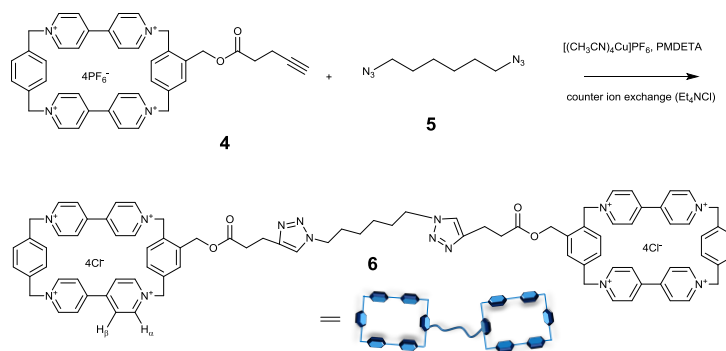

Fig. S2 ^{13}C NMR spectrum of the tri(dialkyloxynaphthalene)-functionalized RAFT agent **3** recorded in CDCl$_3$.

Scheme S1 Strategy for the synthesis of homoditopic tetracationic macrocycle cyclobis(paraquat-*p*-phenylene) host (6).

Synthesis and characterization of the homoditopic tetracationic macrocycle cyclobis(paraquat-*p*-phenylene) (6)

1,6-Diazidohexane **5** (25.5 mg, 0.15 mmol), tetracationic cyclophane cyclobis(paraquat-*p*-phenylene)-alkyne (CBPQT, 4PF$_6$-C≡CH) **4** (1.2 g, 0.99 mmol) and [(CH$_3$CN)$_4$Cu]PF$_6$ (0.19 g, 0.51 mmol) were added to a 25 mL round-bottomed flask equipped with a magnetic stir bar and a Rotaflo® stopcock and the mixture was deoxygenated by argon for 15 min. 9 mL of deoxygenated acetonitrile containing 0.22 mmol of PMDETA were injected with a purged syringe. This mixture was stirred 38 h at 60 °C. The solvent was evaporated to afford a crude product which was dissolved in nitromethane (10 mL). The dropwise addition of a solution of tetraethylammonium chloride (10 mL at 0.9 M) in nitromethane allowed the precipitation of the di(CBPQT^{4+},4Cl$^-$) derivative. The crude product was washed with acetonitrile and dichloromethane and was subjected to column chromatography (SiO$_2$: MeOH/NH$_4$Cl (2M in water)/CH$_3$NO$_2$ (4/2/1.5) (to remove the free CBPQT, 4PF$_6$-C≡CH) and MeOH/NH$_4$Cl (2M in water)/CH$_3$NO$_2$ (2.3/2/3.7)). The fractions containing the product were combined and the eluent was removed in vacuum at 50 °C. The product was dissolved in a minimum of water at 50°C. The dropwise addition of a solution of ammonium hexafluorophosphate in water (1 M) allowed the precipitation of the di(CBPQT^{4+},4PF$_6^-$) derivative. The product was washed with deionized water, diethyl ether and dichlromethane and then dried. The product was dissolved in a minimum of nitromethane. The dropwise addition of a solution of tetraethylammonium chloride (0.9 M) in nitromethane allowed the precipitation of **6**. The product was washed with nitromethane and dichloromethane and then dried under vacuum.
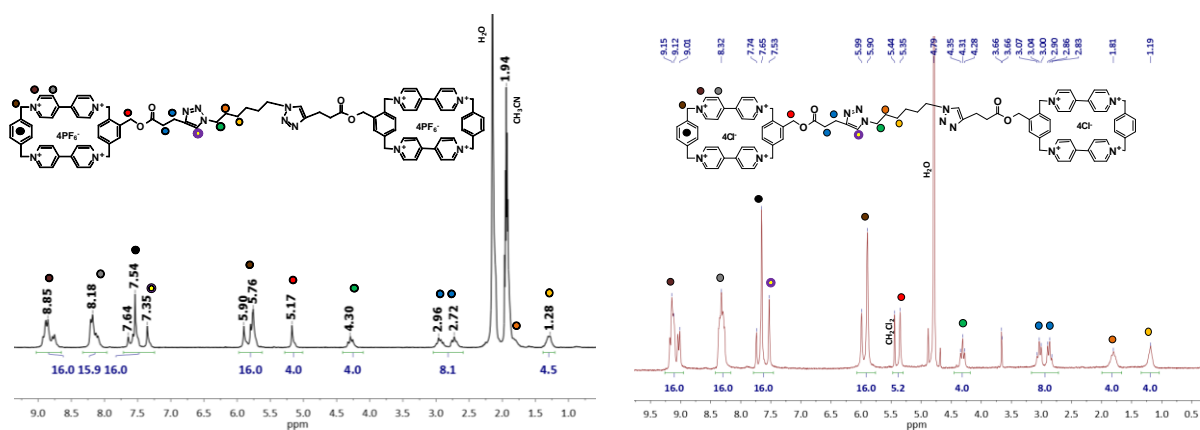
Fig. S3 ^{1}H NMR spectra of the di(CBPQT^{4+}, 4PF6$^-$) recorded in CD$_3$CN (left) and of the di(CBPQT^{4+}, 4Cl$^-$) **6** recorded in D$_2$O (right).
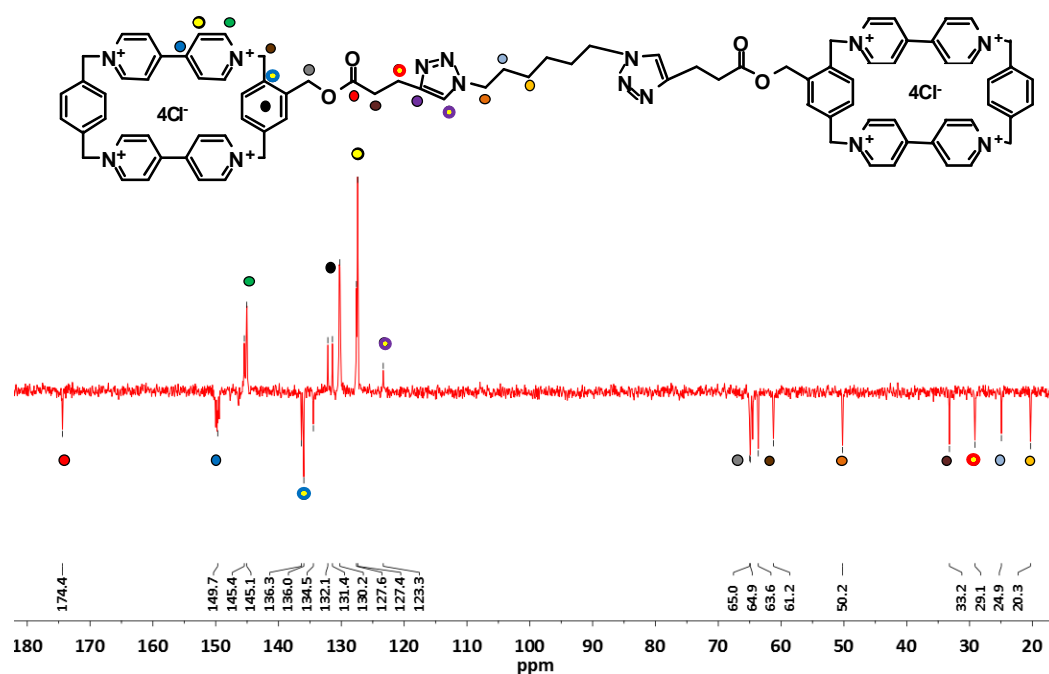

Fig. S4 ^{13}C NMR (JMOD) spectrum of the di(CBPQT^{4+}, 4Cl$^-$) **6** recorded in D$_2$O.

Synthesis and characterization of the end-chain acid-functionalized PDMAc triarm star polymer (P₁)

A round-bottomed flask (25 mL) was loaded with *N,N*-dimethylacrylamide (4.2 g, 42 mmol), tricarboxylic acid-CTA (27.6 mg, 42 µmol) and 1,3,5-trioxane (72 mg, 0.80 mmol). A stock solution of 1,1'-azobis(cyclohexanecarbonitrile) in benzene is prepared (9.8 mg in 40 mL). 8 mL of this solution (equivalent to 8 µmol of initiator) is added to the polymerization solution. The reaction mixture was purged with argon for 45 min in iced water and was then immersed in an oil bath thermostated at 90 °C. Samples were periodically withdrawn via purged syringes to measure the conversion by ^{1}H NMR. After complete drying, the raw polymer from each sample was dissolved in DMF (/LiBr) for size exclusion chromatography analysis. After 90 min at 90°C, the reaction was stopped and the polymer was isolated by precipitation into diethylether, dissolved in water, dialyzed (Spectra/Por® 7, molecular weight cut off: 8 kDa) and lyophilized.

$y = 0.0226x - 0.1279$
$R^2 = 0.9985$
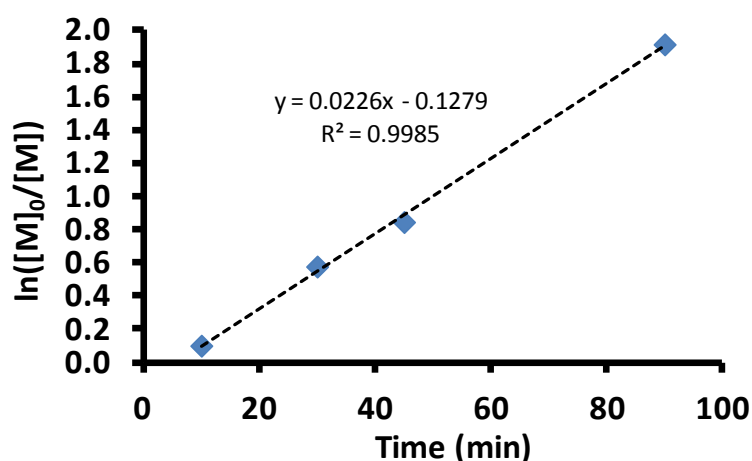
Fig. S5 Semilogarithmic kinetic curve for the RAFT polymerization of DMAc (**P₁**, Table 1)
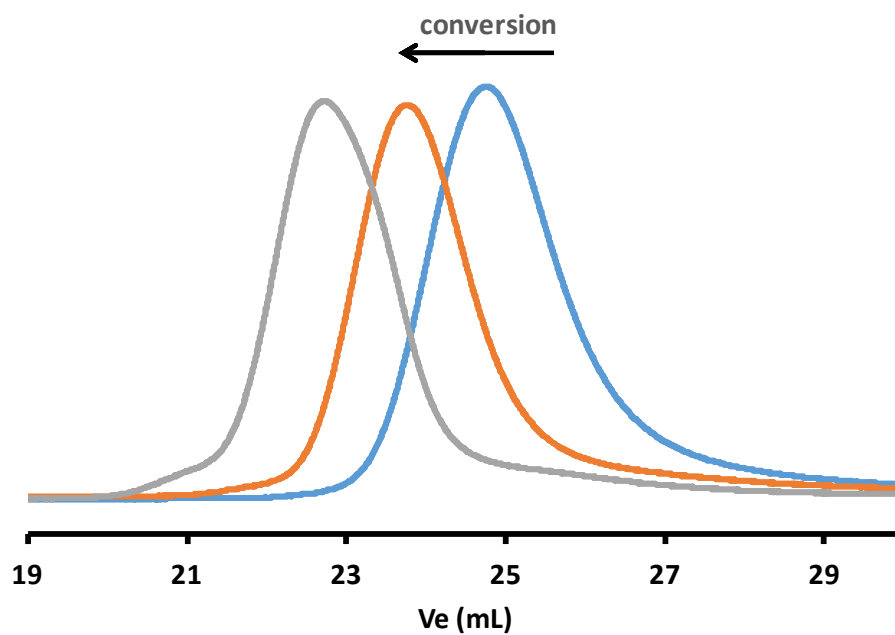
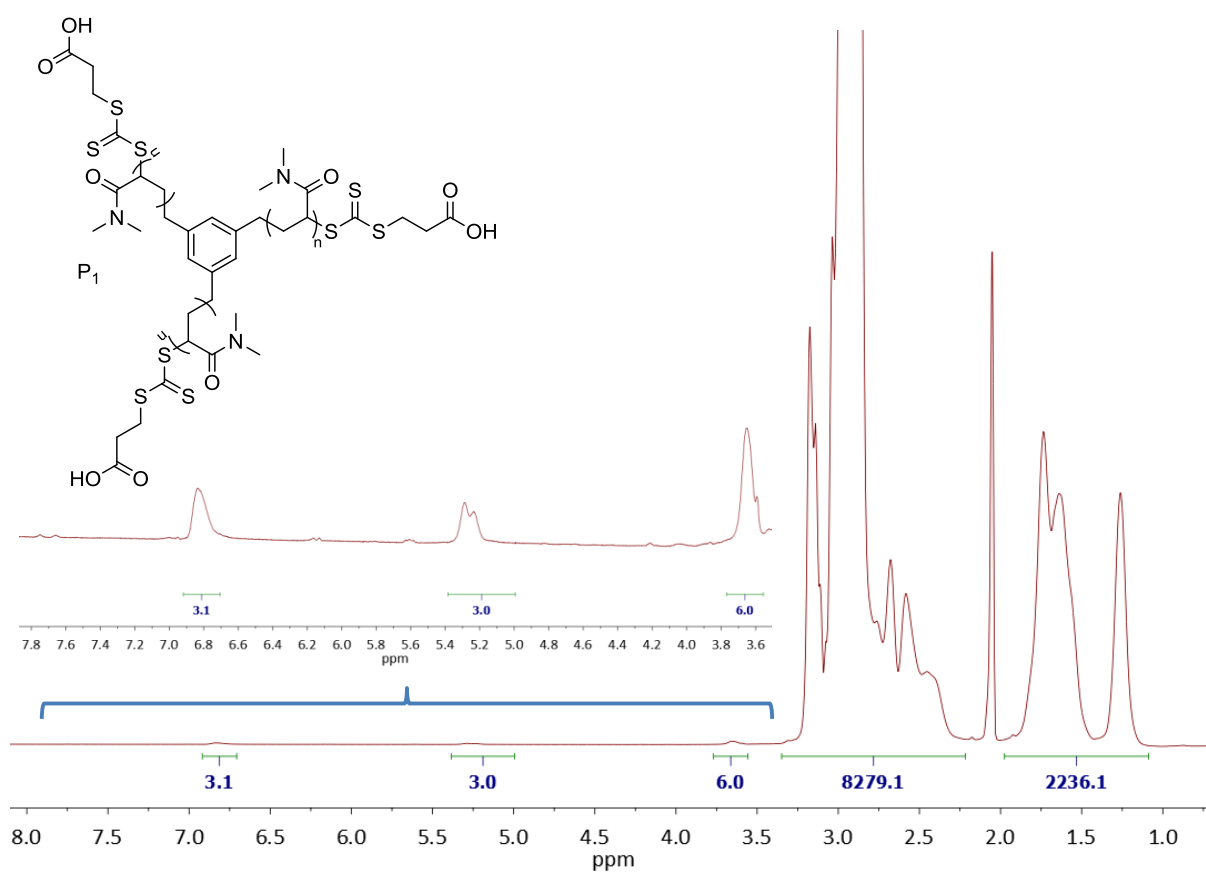**Fig. S6** Size exclusion chromatograms vs. monomer conversion (**P₁**, Table 1).

Fig. S7 ¹H NMR spectrum of the carboxylic acid-functionalized PDMAc triarm star polymer (**P₁**) recorded in acetone_d₆ at 25°C (500 MHz).

Synthesis and characterization of the end-chain dialkyloxynaphthalene-functionalized PDMAc triarm star polymer (P₂)

A round-bottomed flask (25 mL) was loaded with *N,N*-dimethylacrylamide (13.4 g, 135 mmol), tri(dialkyloxynaphthalene)-CTA (107 mg, 64.5 µmol), 1,3,5-trioxane (83 mg, 0.92 mmol), 1,1'-azobis(cyclohexanecarbonitrile) (6.7 mg, 27.4 µmol) and benzene (25 mL). The reaction mixture was purged with argon for 45 min in iced water and was then immersed in an oil bath thermostated at 90 °C. Samples were periodically withdrawn via purged syringes to measure the conversion by ^{1}H NMR. After complete drying, the raw polymer from each sample was dissolved in DMF (/LiBr) for size exclusion chromatography analysis. After 77 min at 90°C, the reaction is stopped and the polymer was isolated by precipitation into diethyl ether, dissolved in water, dialyzed (Spectra/Por® 7, molecular weight cut off: 8 kDa) and lyophilized.
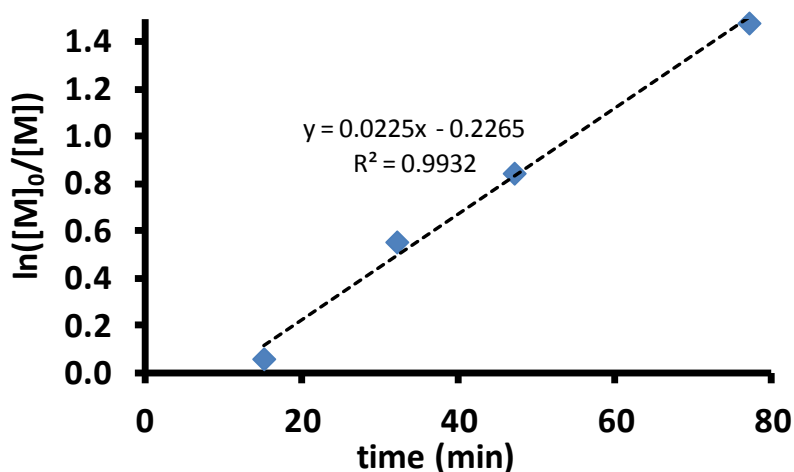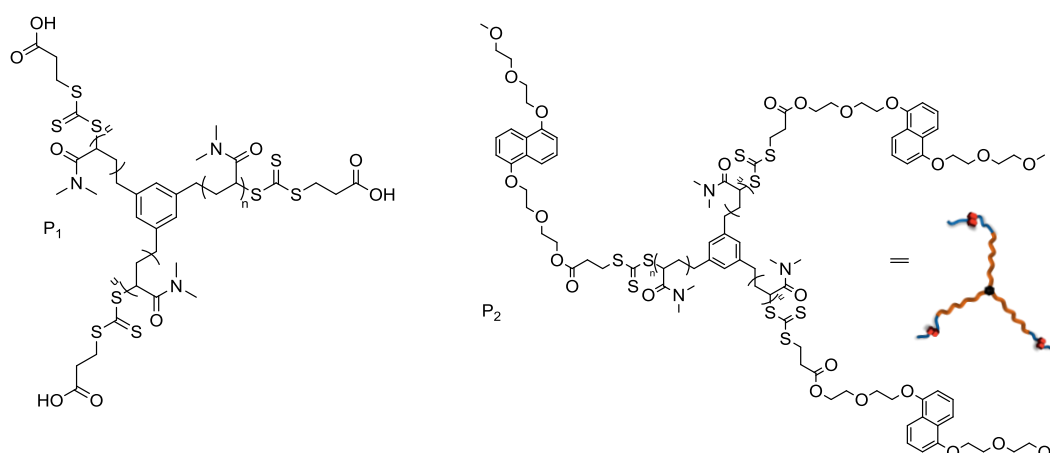

Fig. S8 Semilogarithmic kinetic curve for the RAFT polymerization of DMAc (**P₂**, Table 1)

Scheme S9 Structures of the end-chain carboxylic acid-functionalized and end-chain naphthalene-functionalized PDMAc triarm star polymers.
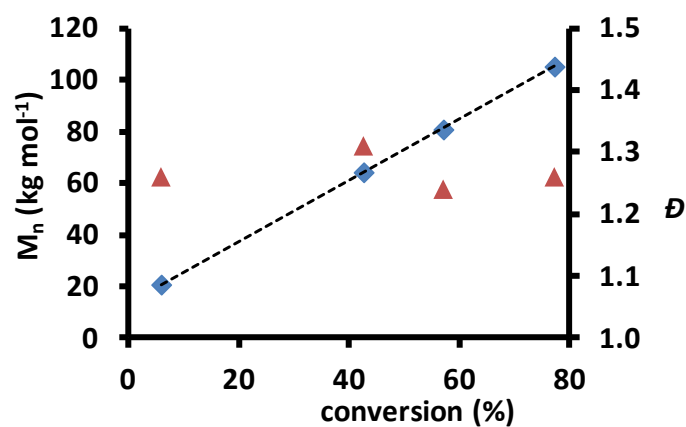

Fig. S10 Evolution of the number-average molar mass, M_n (♦) and dispersity, $Đ$ (▲) determined by SEC in DMF (+ LiBr) using PMMA standards versus monomer conversion for the RAFT polymerization (**P$_2$**) of DMAc at 90 °C.
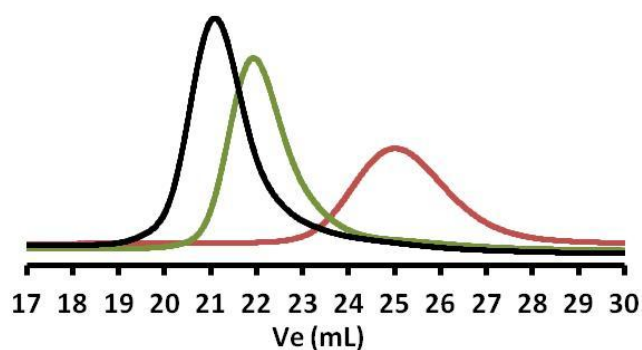

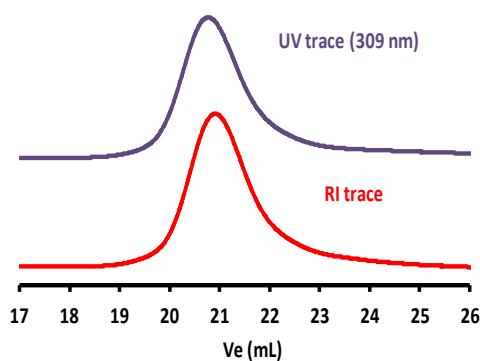**Fig. S11** Size exclusion chromatograms vs. monomer conversion (**P$_2$**, Table 1).

Fig. S12 SEC chromatograms obtained with an UV detector at 309 nm (top) and a refractive index detector (bottom) of end-chain dialkyloxynaphthalene-functionalized PDMAc triarm star polymer after purification (precipitation and dialysis) (**P$_2$**).
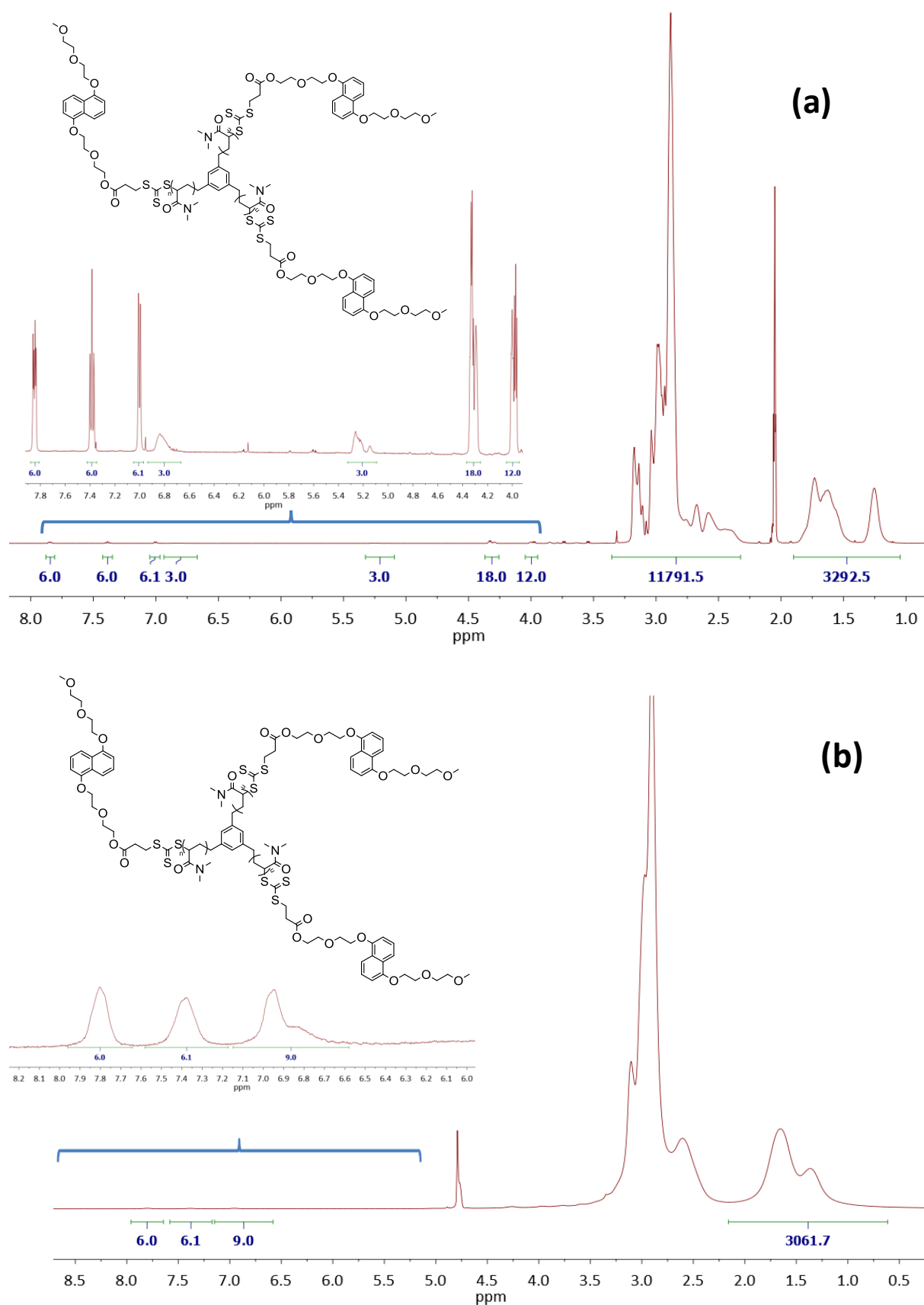
Fig. S13 ^{1}H NMR spectrum of the dialkyloxynaphthalene-functionalized PDMAc triarm star polymer (**P₂**) recorded in acetone_d₆ (a) and in D₂O (b) at 25°C (500 MHz).

dn/dC determination by size exclusion chromatography measurements

The refractive index increment (dn/dC) was measured with the online RI detector by injecting polymer solutions at three different concentrations (3.13, 5.51 and 8.38 mg mL^{-1}). TGA was performed to quantify the weight percentage of remaining solvent in the dried polymer (weight loss (wt %) between 25 and 150°C: 0.58), which allowed the exact sample concentration to be determined. The dn/dC was calculated by plotting the RI area (integrated from the RI signal) versus [$K_{RI}/n_0 \times C \times V_{inj}$] with the OmniSEC software from the slope of the straight line.

$$RI\ Area = K_{RI}/n_0 \times (dn/dC) \times C \times V_{inj}$$

with n_0 = 1.43, the DMF refractive index

K_{RI} = 1.68 ×10^7: refractometer constant

C : the polymer solution concentration

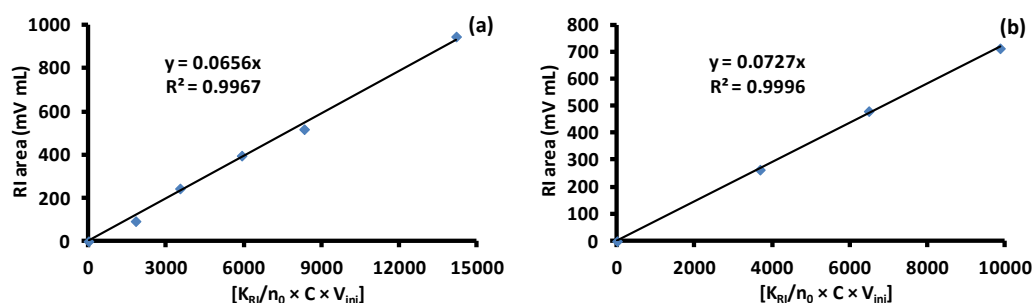V_{inj} : the injection volume of the polymer solution (0.1 mL)

Figure S14. RI area (integrated from the RI signals with Omnisec Software) versus [$K_{RI}/n_0 \times C \times V_{inj}$]. (a): Results obtained from the end-chain carboxylic acid-functionalized PDMAc triarm star polymer, **P$_1$**. (b): Results obtained from end-chain naphthalene-functionalized PDMAc triarm star polymer, **P$_2$**.
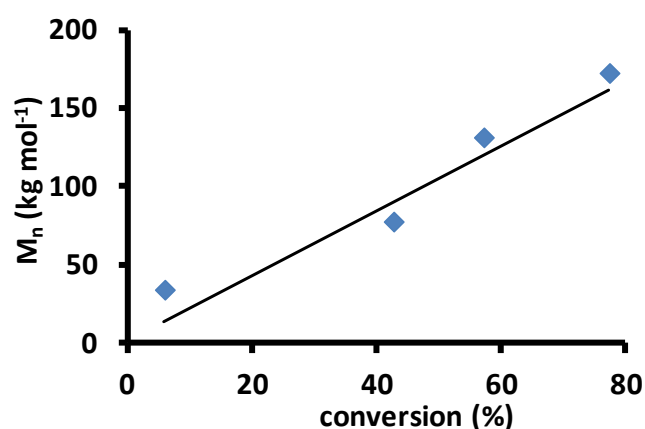

Fig. S15 Evolution of the number-average molar mass based on static light scattering detection, M_n^{LS} (♦), determined using the experimental dn/dC values, versus monomer conversion for the RAFT polymerization (**P$_2$**) of DMAc at 90 °C. The straight line corresponds to the expected evolution of the theoretical number-average molar mass.
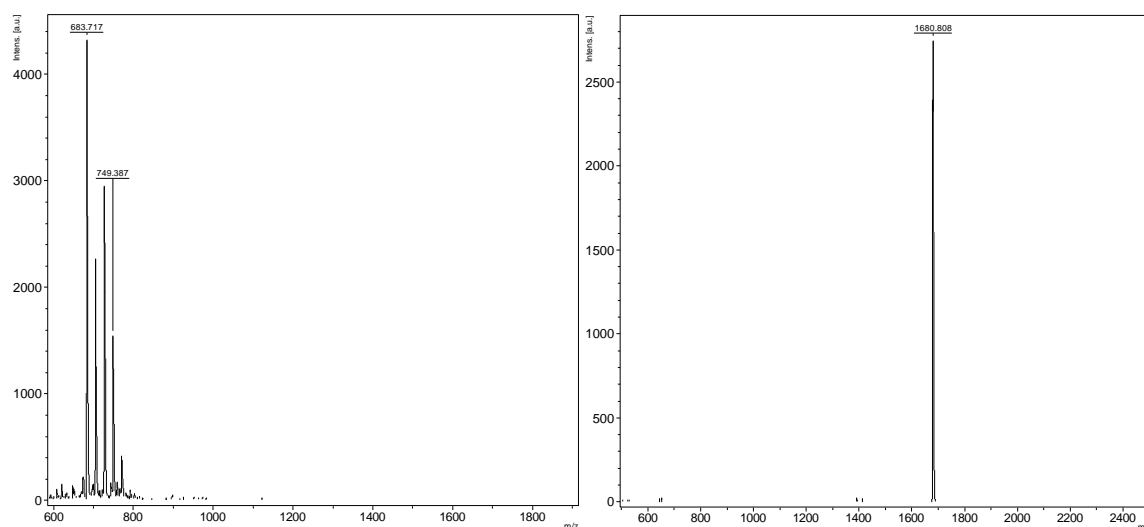
Fig. S16 MALDI-TOF mass spectra with NaI salt/dithranol matrix in linear mode (sum of 1k shots, in positive mode and with a laser repetition rate of 10.5 Hz) of **1** (left) (The three minor populations observed at higher m/z, correspond to the mono, di and tri sodium carboxylate respectively, which have a mass increment of +22, 44, 66 m/z vs the major one) and **3** (right).
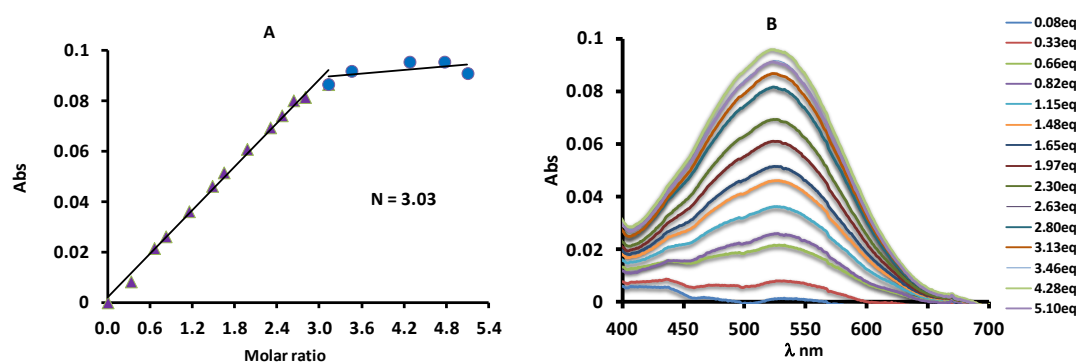

Fig. S17 (A) UV-vis titration experiment of the polymer **P₂** (0.42 mM) with CBPQT[4+]; (B) Dependence of the absorbance at 525 nm versus equivalents of CBPQT[4+] added.

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