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The balance between intramolecular hydrogen bonding, polymer solubility and rigidity in single-chain polymeric nanoparticles†

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A library of copolymers with pendant, protected ureido-pyrimidinone (UPy) groups was prepared applying controlled polymerization techniques. The polymer backbones were based on polyacrylate, polymethacrylate, polystyrene and polynorbornene and differ in stiffness, molecular weight and the linking moiety between the backbone and the UPy group. In all cases, the percentage of protected UPy groups was kept constant. The effect of solvent on the behaviour of the polymers before and after removal of the protecting groups was evaluated in, among others, chloroform and tetrahydrofuran (THF). After deprotection of the UPy protecting group, the UPys dimerize *via* four-fold H-bonding in THF, inducing a collapse into single-chain polymeric nanoparticles (SCPNs), as evidenced by a combination of ^{1}H-NMR spectroscopy, size-exclusion chromatography and dynamic light scattering. In chloroform, on the other hand, dimerization of the UPy groups is present but interchain interactions occur as well, resulting in less-defined SCPNs. Remarkably, the flexibility of the polymer backbone, the polymer molecular weight and the nature of the linker unit all do not affect SCPN formation. In contrast, the interaction between solvent and the UPy moiety is a critical parameter for SCPN formation. For example, strong intramolecular dimerization of the UPys is observed in THF while interparticle interactions are suppressed. From this investigation we conclude that a wide variety of polymer backbones are suitable for polymer collapse *via* supramolecular interactions and thus allow for the formation of SCPNs but that the solvent choice is crucial to enhance intramolecular H-bonding and, at the same time, to suppress interparticle interactions.

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Introduction

The field of supramolecular polymer chemistry has developed from the fusion of classic polymer science and supramolecular chemistry.[1,2] Herein, the creation of functional, highly ordered architectures that combine the excellent material properties of a classic polymer with the reversible and dynamic nature of non-covalent interactions is pursued.[1,3] In the past decade, a number of applications emerged from this interdisciplinary field, ranging from innovative scaffolds for biomedical applications,[4] to electronic devices,[5] and self-healing materials.[6] The seminal work of Stadler[7] and Rotello[8] highlighted the potential of covalent polymers with pendant H-bonding groups, while advances in controlled polymerization techniques triggered renewed interest in the synthesis and application of such "sticky" polymers.[9,10] Recently, the tuneable, highly directional and orthogonal interactions offered by the toolbox of supramolecular chemistry were evaluated to collapse individual chains of synthetic polymers into defined single-chain polymeric nanoparticles (SCPNs).[11] Supramolecular motifs such as diamides,[12] benzene-1,3,5-tricarboxamides (BTAs),[13] ureido-pyrimidinones (UPys),[14] BTA-bipyridines,[15] cucurbit[8]uril,[16] and a combination of thymine–diaminopyridine and six-point cyanuric acid–Hamilton wedge interactions[17] are highly promising for this purpose, but also weak, reversible covalent interactions such as disulfide bridges,[18] or hydrazone groups[19] permit the preparation of dynamic nanoparticles.

In a number of examples, secondary structures mimicking α-helices,[13,15] β-sheets[14a,b] or both[14c] have been observed within the SCPNs, sometimes even when the solvent is water. In fact, the quest for SCPNs that display a compartmentalised, defined three-dimensional shape as a result of a tertiary structure, a feat currently only attainable by DNA and proteins, is a crucial theme. Understanding the rules governing the folding of SCPNs will allow the full potential of supramolecular polymer chemistry to be exploited and the folding of SCPNs will also serve as a simplified model system for understanding protein folding. We

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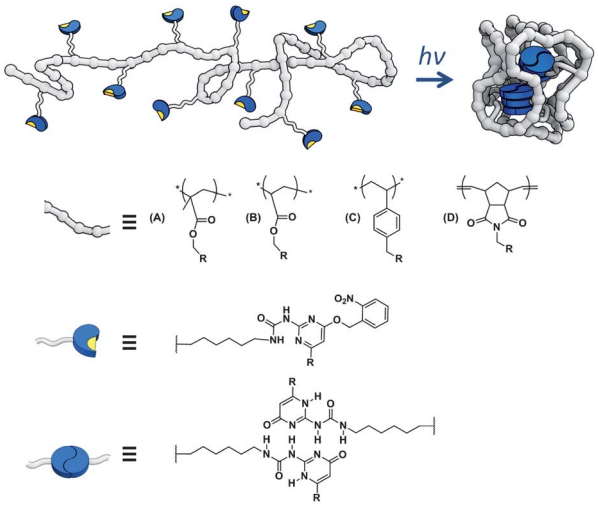


Fig. 1 Schematic representation of the collapse of UPy containing polymers.

envision that these SCPNs will spur novel directions in areas such as catalysis and sensing.[13b,c,15]

While several reports convincingly show the collapse of individual polymer chains into particles of defined, nanometer-sized dimensions, the relation between the nature of the polymer backbone (stiffness, solubility), the H-bonding group and its collapse behaviour has not been addressed. Recent theoretical calculations by Markvoort *et al.* showed the critical importance of chain-flexibility on the collapse of single-polymer chains.[20] A deeper understanding of this relationship is imperative for the design of future, functional SCPNs.

In this contribution, we systemically investigate the formation of SCPNs as a function of polymer backbone, polymer length, nature of the connecting linker and solvent. We select four of the most widely used polymer backbones in side-chain functionalised supramolecular polymers: poly *n*-butylacrylate and polymethyl methacrylate which have a relatively flexible backbone and the more stiff polystyrene and polynorbornene. In all cases, we select 2-ureido-pyrimidinone (UPy) units as self-assembling moieties because of their ability to dimerise *via* strong four-fold hydrogen bonds ($K_{dim} = 6 \times 10^7$ mol L^{-1} in chloroform).[21] The application of a UV-labile *o*-nitrobenzyl-protecting group to temporarily "cage" the UPy enhances the solubility of the polymer constructs and allows initiating of folding of the individual polymer chains on demand by UV irradiation (Fig. 1).[14,22] With the help of size exclusion chromatography (SEC) and dynamic light scattering (DLS), we evaluate the importance of solvent, polymer molecular weight, spacer length between UPy and polymer and the stiffness of the polymer in the folding behaviour of the SCPNs. The results indicate that, of all the parameters we anticipated to be involved in SCPN folding, SCPN–solvent interactions are by far the most important one.

Experimental section

Materials and methods

Commercial reagents were obtained from Acros or Sigma-Aldrich. Solvents were obtained from Biosolve. Deuterated solvents were obtained from Cambridge Isotope Laboratories. Styrene was distilled under reduced pressure prior to use, methyl methacrylate, 2-((trimethylsilyl)oxy)ethyl methacrylate and *n*-butylacrylate were passed through a short column filled with an inhibitor remover (Aldrich) or basic alumina. AIBN was recrystallized from methanol. Dry, degassed toluene, THF and dichloromethane were tapped off a solvent purification column. Chloroform was dried over molecular sieves and triethylamine was stored over KOH pellets. All other commercial chemicals were used as received. 4-Cyano-4-methyl-5-(phenylthio)-5-thioxopentanoic acid was kindly provided by SyMO-Chem (Eindhoven, the Netherlands). Aminomethylated polystyrene resin was obtained from NovaBioChem. *N*-(6-Methyl-4-oxo-1,4-dihydropyrimidin-2-yl)-1*H*-imidazole-1-carboxamide (**1a**),[23] *N*-(4-oxo-6-tridecyl-1,4-dihydropyrimidin-2-yl)-1*H*-imidazole-1-carboxamide (**1b**),[24] *tert*-butyldimethyl(4-vinylbenzyloxy) silane (**9**),[25] (*N*-dodecyl)-5-norbornene-*exo*-2,3-dicarboximide,[26] *N*-acetyloxy-2,5-(pyrrolidinedione)-5-norbornene-*exo*-2,3-dicarbox-imide,[27] 4-vinylbenzyl-6-(*tert*-butoxycarbonylamino)hexanoate,[25] and 3rd generation Grubbs catalyst (dichloro[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene](benzylidene)-bis-(pyridine)ruthenium(II))[28] were prepared according to literature procedures. NMR spectroscopy was performed on a Varian Mercury Vx 400 MHz and/or a Varian 400 MR 400 MHz (400 MHz for ^{1}H and 100 MHz for ^{13}C). To improve the signal to noise ratio, typical measurements on polymer samples were carried out with 3000 scans and a delay time of 5 seconds. Deuterated solvents used are indicated in each case. ^{1}H chemical shifts are reported in ppm downfield from tetramethylsilane (TMS), ^{13}C chemical shifts in ppm downfield of TMS using the resonance of the deuterated solvent as internal standard. Abbreviations used are s: singlet, d: doublet, dd: double doublet, t: triplet, q: quartet, and m: multiplet. Matrix assisted laser desorption/ionization (MALDI) mass spectra were obtained on PerSeptive Biosystems Voyager DE-PRO or Bruker MALDI-TOF spectrometers using α-cyano-4-hydroxycinnamic acid (CHCA) and 2-[(2*E*)-3-(4-*tert*-butylphenyl)-2-methylprop-2-enylidene]-malononitrile (DCTB) as matrices. GC-MS measurements were performed on a Shimadzu GC-MS system equipped with an autosampler with a Zebron ZB-35 column of 30 m × 0.25 mm with a 0.25 μm coating and using the following temperature program: 80 °C| 1 min → 330 °C, 30 °C min^{-1}|3 min. Manual column chromatography was performed using Merck 60 Å pore size silica gel (particle size: 63–200 μm). Flash chromatography was performed using an automatic flash chromatography instrument Biotage Isolera One equipped with Biotage SNAP Cartridge KP-Sil silica cartridges. IR spectroscopy was performed on a Perkin-Elmer FTIR Spectrum 2 equipped with a Perkin-Elmer UATR Two accessory. Dynamic light scattering measurements were performed on a Malvern μV Zetasizer equipped with an 830 nm laser and a scattering angle of 90° at a temperature of 20 °C. Samples were prepared by filtering solutions through a 0.2 μm PTFE-filter (Whatman) in a fluorescence cell with a path length of 1 cm. DMF-SEC measurements were carried out in PL-GPC-50 plus from Polymer Laboratories (Agilent Technologies) with the refractive index detector working in DMF containing 10 mM LiBr at 50 °C at a constant flow rate of 1 mL min^{-1} on a Shodex

GPC-KD-804 column (exclusion limit = 400 000 Da; 0.8 cm i.d. × 300 mL) which was calibrated with polyethyleneoxide (PEO) samples with a range from 282–77 350 Da (Polymer Laboratories – Agilent Technologies). THF-SEC-measurements were performed on a Shimadzu-system with two Agilent Technology columns in series (PLgel 5 μm mixed C [200–2 000 000 Da] and PLgel 5 μm mixed D [200–40 000 Da]) and equipped with a RI detector (Shimadzu RID-10A) and a PDA detector (Shimadzu SPD-M10A), with THF as eluent at a constant flow rate of 1.0 mL min^{-1}. The system was calibrated with polystyrene (PS) samples with a range of 580–100 000 Da (Polymer Laboratories). $CHCl_3$-SEC-measurements were performed on a Shimadzu-system equipped with an Agilent Technology Resipore column [200–400 000 Da] and equipped with a RI detector (Shimadzu RID-10A) and a PDA detector (Shimadzu SPD-M20A), with $CHCl_3$ as eluent at a constant flow rate of 1.0 mL min^{-1}. The system was calibrated with polystyrene (PS) samples with a range of 92–371 000 Da. SEC-measurements were performed on purified polymers on a THF-system, unless otherwise noted. All measurements shown for $CHCl_3$ and THF-measurements were those recorded with the PDA-detector. Photoirradiation experiments were performed in a Luzchem LZC-4V UV reactor equipped with 8 × 8 watt UV-A light bulbs (λ_{max} = 350 nm). The photoirradiation reactions were performed in a quartz cuvette or NMR tube at room temperature.

Synthesis of UPy-building blocks

***tert*-Butyl 6-(3-(4-oxo-6-tridecyl-1,4-dihydropyrimidin-2-yl) ureido)hexylcarbamate (2b).** *N*-(4-Oxo-6-tridecyl-1,4-dihydropyrimidin-2-yl)-1*H*-imidazole-1-carboxamide (0.246 g, 0.635 mmol) and *tert*-butyl 6-aminohexylcarbamate (1.1 eq., 0.151 g, 0.698 mmol) were dissolved in 20 mL $CHCl_3$ and refluxed overnight under Ar. After the reaction was completed, the mixture was transferred to a separation funnel and the organic phase was washed with 1 M HCl (40 mL), $NaHCO_3$ (sat., 40 mL) and brine (40 mL). The solvent was removed *in vacuo* and the product was obtained as a white solid (0.330 g, 97%). ^{1}H-NMR ($CDCl_3$): δ = 13.11 (s, 1H, N–*H*), 11.83 (s, 1H, N–*H*), 10.09 (s, 1H, N–*H*), 5.83 (s, 1H, Ar–*H*), 4.60 (s, 1H, O–CO–N–*H*), 3.22 (q, 2H, NH–CH_2), 3.04 (q, 2H, O–CO–NH–CH_2), 2.45 (t, 2H, Ar–CH_2), 1.86–1.08 (m, 39H, CH_2), 0.87 (t, 3H, CH_3). ^{13}C-NMR ($CDCl_3$): δ = 173.3, 156.6, 156.0, 154.7, 152.5, 110.0, 105.9, 40.4, 39.8, 32.7, 31.9, 29.9, 29.7, 29.6, 29.6, 29.6, 29.5, 29.4, 29.4, 29.2, 28.9, 28.5, 27.0, 26.4, 26.3, 22.7, 14.1. MALDI-TOF-MS: *m*/*z*: 536.28 (M + H^+).

***tert*-Butyl 6-(3-(4-(2-nitrobenzyloxy)-6-tridecylpyrimidin-2-yl) ureido)hexylcarbamate (3b).** Compound **2b** (0.200 g, 0.373 mmol) was dissolved in 10 mL of dry DMF, 1-(chloromethyl)-2-nitrobenzene (1.5 eq., 0.096 g, 0.56 mmol) and K_2CO_3 (1.6 eq., 0.083 g, 0.597 mmol) were added and the mixture was heated at 80 °C under Ar for 24 h. The reddish-brown mixture was concentrated *in vacuo* and 10 mL H_2O and 10 mL $CHCl_3$ were added. The layers were separated and the water layer was extracted with $CHCl_3$ (20 mL). The organic layers were combined and washed with brine (20 mL). The product was purified by column chromatography (heptane–CH_2Cl_2; gradient from 0% CH_2Cl_2 to 100% CH_2Cl_2, followed by CH_2Cl_2–methanol; gradient from 0% methanol to 5% methanol), to yield the title compound as a slightly yellow solid (0.220 g, 88%). ^{1}H-NMR ($CDCl_3$): δ = 9.14 (s, 1H, N–*H*), 8.10 (d, 1H, Ar–*H*), 7.64 (d, 2H, Ar–*H*), 7.55–7.41 (m, 1H, Ar–*H*), 6.99 (s, 1H, N–*H*), 6.21 (s, 1H, Ar–*H*), 5.73 (s, 2H, Ar–CH_2–O), 4.47 (s, 1H, O–CO–N–*H*), 3.31 (q, 2H, NH–CH_2), 3.05 (q, 2H, O–CO–NH–CH_2), 2.58 (t, 2H, Ar–CH_2), 1.76–1.17 (m, 39H), 0.87 (t, 3H, CH_3). ^{13}C-NMR ($CDCl_3$): δ = 169.6, 157.3, 155.9, 154.1, 147.6, 133.7, 132.4, 129.0, 128.7, 125.0, 99.7, 76.7, 64.7, 40.5 39.8, 37.3, 31.9, 30.0, 29.8, 29.7, 29.7, 29.7, 29.5, 29.5, 29.4, 29.2, 28.4, 28.2, 26.7, 26.5, 22.7, 14.1. MALDI-TOF-MS: *m*/*z*: 671.42 (M + H^+).

1-(6-Aminohexyl)-3-(4-(2-nitrobenzyloxy)-6-tridecylpyrimidin-2-yl)urea (4b). Compound **3b** (0.106 g, 0.158 mmol) was dissolved in trifluoroacetic acid (TFA, 0.5 mL) and CH_2Cl_2 (10 mL), the solution was stirred overnight under Ar. The solvent and excess of TFA were removed *in vacuo* using co-evaporation with toluene. The product was dissolved in $CHCl_3$ (20 mL) and washed with 1 M NaOH (aq., 20 mL) and brine (20 mL). The solvent was removed *in vacuo* to give the title compound as a slightly yellow solid (0.089 g, 99%). ^{1}H-NMR ($CDCl_3$): δ = 9.15 (s, 1H, N–*H*), 8.10 (d, 1H, Ar–*H*), 7.65 (d, 2H, Ar–*H*), 7.55–7.43 (m, 1H, Ar–*H*), 6.98 (s, 1H, N–*H*), 6.26 (s, 1H, Ar–*H*), 5.73 (s, 2H, Ar–CH_2–O), 3.33 (q, 2H, NH–CH_2), 2.68 (t, 2H, NH_2–CH_2), 2.60 (t, 2H, Ar–CH_2), 1.79–1.16 (m, 30H), 0.88 (t, 3H, CH_3). ^{13}C-NMR ($CDCl_3$): δ = 169.6, 157.3, 154.1, 147.6, 133.7, 132.4, 129.0, 128.7, 125.0, 99.7, 64.7, 42.2, 39.9, 37.3, 33.9, 31.9, 29.9, 29.7, 29.7, 29.7, 29.7, 29.5, 29.5, 29.4, 29.2, 28.2, 26.9, 26.6, 22.69, 14.12. MALDI-TOF-MS: *m*/*z*: 571.44 (M + H^+).

1-(6-Isocyanatohexyl)-3-(4-(2-nitrobenzyloxy)-6-tridecyl pyrimidin-2-yl)urea (5b). A solution of **4b** (89 mg, 0.156 mmol) in 2 mL dry $CHCl_3$ was quickly injected into a solution of di-*tert*-butyltricarbonate (40.9 mg, 0.156 mmol) in dry $CHCl_3$ (15 mL). The mixture was stirred at room temperature overnight under Ar. The solvent was removed *in vacuo* and the product was obtained as a slightly yellow solid (0.092 g, 99%). ^{1}H-NMR ($CDCl_3$): δ = 9.18 (s, 1H, N–*H*), 8.13 (d, 1H, Ar–*H*), 7.65 (d, 2H, Ar–*H*), 7.50 (m, 1H, Ar–*H*), 7.02 (s, 1H, N–*H*), 6.26 (s, 1H, Ar–*H*), 5.73 (s, 2H, Ar–CH_2–O), 3.50–3.16 (m, 4H, NH–CH_2, OCN–CH_2), 2.60 (t, 2H, Ar–CH_2), 1.82–1.12 (m, 30H, CH_2), 0.88 (t, 3H, CH_3). ^{13}C-NMR ($CDCl_3$): 171.9, 169.7, 157.5, 154.6, 154.4, 147.7, 133.8, 132.5, 129.2, 128.8, 125.1, 99.8, 64.8, 43.02, 39.9, 37.4, 32.0, 31.3, 29.9, 29.8, 29.7, 29.6, 29.5, 29.3, 28.5, 28.3, 26.5, 26.4, 26.3, 26.1, 22.8, 14.2. MALDI-TOF-MS: *m*/*z*: 597.23 (M + H^+).

1-(6-Isocyanatohexyl)-3-(4-methyl-6-((2-nitrobenzyl)oxy)-pyrimidin-2-yl)urea (5a). The synthesis of **5a** was performed in analogy to that of **5b**.

^{1}H-NMR ($CDCl_3$): δ = 9.12 (s, 1H, N–*H*), 8.13 (d, 1H, Ar–*H*), 7.65 (d, 2H, Ar–*H*), 7.50 (m, 1H, Ar–*H*), 7.03 (s, 1H, N–*H*), 6.28 (s, 1H, Ar–*H*), 5.73 (s, 2H, Ar–CH_2–O), 3.38–3.08 (m, 4H, NH–CH_2, OCN–CH_2), 2.37 (s, 3H, Ar–CH_3), 1.73–1.28 (m, 8H, CH_2). ^{13}C-NMR ($CDCl_3$): δ = 169.5, 157.3, 154.3, 154.1, 147.6, 133.7, 132.4, 128.9, 128.7, 125.0, 100.2, 64.7, 42.9, 39.8, 31.2, 29.7, 26.4, 26.2, 23.8. MALDI-TOF-MS: *m*/*z*: 429.31 (M + H^+).

6-((*tert*-Butoxycarbonyl)amino)hexyl (6-(3-(4-methyl-6-((2-nitrobenzyl)oxy)pyrimidin-2-yl)ureido)hexyl)-carbamate (6). Compound **5a** (0.300 g, 0.700 mmol), *tert*-butyl-6-hydroxyhexylcarbamate (0.160 g, 0.735 mmol) and a drop of dibutyltin

dilaureate (DBTDL) were dissolved in $CHCl_3$ (15 mL). The resulting mixture was refluxed under Ar for 48 h. Some silica was added and the mixture was refluxed under Ar for another 3 hours. The solution was filtered, the solvent removed *in vacuo* and the crude product purified with flash column chromatography (eluent: ethylacetate–*n*-heptane) to obtain a slightly yellow solid (0.370 g, 82%). ^{1}H-NMR ($CDCl_3$): $\delta = 9.13$ (s, 1H, N–*H*), 8.12 (d, 1H, Ar–*H*), 7.65 (d, 2H, Ar–*H*), 7.50 (m, 1H, Ar–*H*), 7.16 (s, 1H, N–*H*), 6.28 (s, 1H, Ar–*H*), 5.74 (s, 2H, Ar–CH_2–O), 4.73 (s, 1H, N–*H*), 4.52 (s, 1H, N–*H*), 3.63 (t, 2H, OCO–CH_2), 3.31 (m, 2H, NH–CH_2), 3.11 (m, 4H, O–CO–NH–CH_2), 2.37 (s, 3H, Ar–CH_3), 1.70–1.22 (m, 25H, CH_3, CH_2). ^{13}C-NMR ($CDCl_3$): $\delta =$ 169.5, 157.3, 156.8, 156.0, 154.1, 133.7, 132.4, 128.9, 128.7, 125.0, 100.2, 78.9, 64.7, 62.7, 40.5, 40.4, 39.7, 32.6, 30.1, 29.9, 29.7, 28.9, 28.4, 26.7, 26.4, 23.8. *m*/*z*: 646.42 ($M + H^+$).

6-Aminohexyl (6-(3-(4-methyl-6-((2-nitrobenzyl)oxy)pyrimidin-2-yl)ureido)hexyl)carbamate-TFA salt (7). Compound **6** (0.080 g, 0.124 mmol) was dissolved in CH_2Cl_2 (2 mL), 0.5 mL TFA was added and the mixture was stirred for 45 min at room temperature. The solvent and excess of TFA were removed *in vacuo* using co-evaporation with toluene. The resulting product, a slightly yellow oil, was used without further purification. ^{1}H-NMR ($CDCl_3$): $\delta = 8.94$ (s, 1H, N–*H*), 7.91 (s, broad, N–H_3^+), 8.08 (d, 1H, Ar–*H*), 7.65 (d, 2H, Ar–*H*), 7.53 (m, 1H, Ar–*H*), 6.32 (s, 1H, Ar–*H*), 5.86 (s, 2H, Ar–CH_2–O), 4.79 (s, 1H, N–*H*), 4.06 (s, 1H, N–*H*), 3.64 (m, 2H, OCO–CH_2), 3.30 (m, 2H, NH–CH_2), 3.15 (m, 2H, O–CO–NH–CH_2), 2.44 (s, 3H, Ar–CH_3), 1.77–1.23 (m, 16H, CH_2). ^{19}F-NMR ($CDCl_3$): $\delta = -75.8$. MALDI-TOF-MS: *m*/*z*: 546.44 (M-$C_2F_3O_2^+$).

Synthesis of additional monomers

4-((*tert*-Butyldimethylsilyl)oxy)butyl acrylate. Imidazole (4.8 g; 0.070 mol), 4-hydroxybutylacrylate (5.0 g; 0.035 mol) and *tert*-butylchlorodimethylsilane (5.3 g; 0.035 mol) were dissolved in dry DMF (50 mL). The mixture was stirred overnight at room temperature under Ar and then poured into water (400 mL) and extracted with diethylether (3 × 100 mL). The organic layers were collected, dried with $MgSO_4$ and the solvent was removed *in vacuo*. The crude product was purified with column chromatography in $CHCl_3$ to yield the title compound as a slightly yellow liquid (5.2 g, 58%). ^{1}H-NMR ($CDCl_3$): $\delta = 6.39$ (dd, $J =$ 17.3, 1.3 Hz, 1H, C=C–*H*), 6.11 (dd, $J = 17.3$, 10.4 Hz, 1H, CO–C*H*=CH_2), 5.80 (dd, $J = 10.4$, 1.4 Hz, 1H, C=C–*H*), 4.17 (t, 2H, CO–O–CH_2), 3.63 (t, 2H, Si–O–CH_2), 1.72 (q, 2H, CH_2), 1.58 (q, 2H, CH_2), 0.88 (s, 9H, Si–C–CH_3), 0.04 (s, 6H, Si–CH_3). ^{13}C-NMR ($CDCl_3$): $\delta = 166.3$, 130.4, 128.6, 64.5, 62.6, 31.9, 29.2, 25.9, 25.2, −5.4. GC/MS $t_R = 4.508$; *m*/*z*: 129.

6-((*tert*-Butoxycarbonyl)amino)hexyl methacrylate. *tert*-Butyl (6-hydroxyhexyl)carbamate (2.00 g, 9.20 mmol) and triethylamine (1.2 eq., 1.12 g, 11.1 mmol) were dissolved in $CHCl_3$ (50 mL). The solution was cooled to 0 °C, and methacryloyl chloride (1.05 eq., 1.01 g, 9.66 mmol) in 5 mL $CHCl_3$ was slowly added to the solution. After addition was complete, the mixture was stirred overnight under Ar. The reaction mixture was transferred to a separation funnel, water (60 mL) was added and the water layer was extracted with $CHCl_3$ (3 × 30 mL), the combined organic layers were washed with HCl (0.1 M, 1 × 30 mL) and $NaHCO_3$ (sat, 1 × 30 mL) and finally dried with Na_2SO_4. The solvent was removed *in vacuo* to obtain a colourless liquid (2.05 g, 78%). ^{1}H-NMR ($CDCl_3$): $\delta = 6.08$ (s, 1H, C=C–*H*), 5.54 (s, 1H, C=C–*H*), 4.50 (s, 1H, N–*H*), 4.13 (t, 2H, O–CH_2), 3.10 (t, 2H, N–CH_2), 1.93 (s, 3H, C=C–CH_3), 1.72–1.26 (m, 17H, CH_2). ^{13}C-NMR ($CDCl_3$): $\delta =$ 167.5, 156.0, 136.5, 125.2, 79.1, 64.6, 40.5, 30.0, 28.5, 28.4, 26.4, 25.7, 18.3.

Synthesis of polymers

P1a. A Schlenk tube was charged with methyl methacrylate (MMA, 0.900 g, 8.99 mmol), 2-((trimethylsilyl)oxy)ethyl methacrylate (HEMA-TMS, 0.202 g, 1.00 mmol), 4-cyano-4-methyl-5-(phenylthio)-5-thioxopentanoic acid (9.748 mg, 0.0349 mmol) and azobis-isobutyronitrile (20% to CTA, 1.09 mg, 6.5 μmol) and 4 mL dioxane. The mixture was subjected to 3 freeze–pump–thaw cycles, backfilled with argon and placed in a pre-heated oil bath at 60 °C. After 47 h the polymerization was stopped by placing the reactor in a liquid-nitrogen bath. The polymer was purified by precipitation in MeOH, filtered and dried under high vacuum at room temperature to a constant weight to obtain a pink powder. ^{1}H-NMR ($CDCl_3$): $\delta = 4.12$ (s, broad, CO–O–CH_2), 3.86 (s, broad, CH_2–O–Si), 3.61 (s, broad, CO–O–CH_3), 2.09–0.79 (m, CH_2, CH_3), 0.16 (s, Si–CH_3). SEC: $M_n = 21.2$ kDa, PDI = 1.07.

P1b. Cu(0) wire ($d = 1$ mm, $L = 60$ cm), 2-cyano-2-propyl benzodithioate (7.6 mg, 34.4×10^{-3} mmol), HEMA-TMS (0.6 mL, 2.75 mmol) and anisole (3.2 mL) were charged in a Schlenk flask. The flask was deoxygenated with N_2 for 30 minutes. MMA (deoxygenated with N_2 for 30 minutes, 2.65 mL, 24.8 mmol) was added. CuBr (5.02×10^{-2} mg, 3.5×10^{-4} mmol) and TPMA (0.305 mg, 1.05×10^{-3} mmol) in 0.05 mL anisole (deoxygenated with N_2 for 30 minutes) were added and the flask was placed in a pre-heated oil bath at 80 °C for 18 hours. The polymer was purified by precipitation in MeOH, filtered and dried under high vacuum at room temperature to a constant weight to obtain a slightly pink powder. The spectroscopic data obtained were identical to those of **P1a**. SEC: $M_n = 59.4$ kDa, PDI = 1.14.

P1c. A Schlenk tube was charged with methyl methacrylate (0.990 g, 9.89 mmol), 6-((*tert*-butoxycarbonyl)amino)hexyl methacrylate (0.314 g, 1.10 mmol), 4-cyano-4-methyl-5-(phenylthio)-5-thioxopentanoic acid (10.279 mg, 0.0368 mmol) and azobis-isobutyronitrile (20% to CTA, 1.19 mg, 7.2 μmol) and 4 mL dioxane. The mixture was subjected to 3 freeze–pump–thaw cycles, backfilled with argon and placed in a pre-heated oil bath at 60 °C. After 63 h the polymerization was stopped by placing the reactor in a liquid nitrogen bath. The polymer was purified by precipitation in MeOH, filtered and dried under high vacuum at room temperature to a constant weight to obtain a pink powder. ^{1}H-NMR ($CDCl_3$): $\delta = 4.71$ (s, N–*H*), 3.94 (s, broad, CO–O–CH_2), 3.60 (s, broad, CO–O–CH_3), 3.12 (s, broad, N–CH_2), 2.09–0.79 (m, CH_2, CH_3). SEC: $M_n = 28.0$ kDa, PDI = 1.20.

P2. A Schlenk tube was charged with *n*-butylacrylate (1.00 g, 7.80 mmol) and 4-((*tert*-butyldimethylsilyl)oxy)butyl acrylate (0.202 g, 0.782 mmol). To this mixture, *N*-*tert*-butyl-*N*-(2-methyl-1-phenylpropyl)-*O*-(1-phenylethyl)hydroxylamine (1/250 eq. to total amount of acrylates, 11.1 mg, 3.84×10^{-2} mmol) and

2,2,5-trimethyl-4-phenyl-3-azahexane-3-nitroxide (1/1250 eq. to total amount of acrylates, 0.447 mg, 1.7 μmol) were added. The mixture was subjected to 5 consecutive freeze–pump–thaw cycles, backfilled with argon and placed in a pre-heated oil bath at 125 °C. After 23 h the polymerization was stopped by placing the reactor in an ice bath. The polymer was purified by precipitation in MeOH–H_2O, 5 : 95, the solvent decanted and the polymer dried under high vacuum at room temperature to a constant weight to obtain a very viscous, slightly yellow oil. ^{1}H-NMR ($CDCl_3$): δ = 4.02 (t, broad, CO–O–CH_2), 3.62 (t, Si–O–CH_2), 2.38–1.30 (m, CH, CH_2), 0.92 (t, CH_3), 0.88 (s, Si–C–CH_3), 0.04 (s, Si–CH_3). SEC: M_n = 34.8 kDa, PDI = 1.83.

General procedure for the synthesis of P3a and P3b. P3a and **P3b** were synthesized following literature procedures:[25] **P3a** ^{1}H-NMR ($CDCl_3$): δ = 7.33–6.18 (m, Ar–H), 4.61 (s, broad, Ar–CH_2), 2.21–1.19 (m, CH, CH_2), 0.94 (s, Si–C–(CH_3)$_3$), 0.07 (s, Si–(CH_3)$_2$). SEC: M_n = 19 000, PDI = 1.08.

P3b ^{1}H-NMR ($CDCl_3$): δ = 7.20–6.24 (m, Ar–H), 4.97 (s, Ar–CH_2–O–CO), 4.45 (s, N–H), 3.05 (s, broad, CO–NH–CH_2), 2.32 (s, broad, O–CO–CH_2), 2.16–1.20 (m, CH, CH_2). SEC: M_n = 18 100, PDI = 1.10.

P4. A Schlenk tube was charged with (*N*-dodecyl)-5-norbornene-*exo*-2,3-dicarboximide (90.8 mg, 0.274 mmol), (*N*-acetyloxy-2,5-pyrrolidinedione)-5-norbornene-*exo*-2,3-dicarbox-imide (9.62 mg, 0.0300 mmol) and 3 mL dichloromethane. The mixture was placed in an oil bath at 30 °C. Oxygen was removed by bubbling Ar for 0.5 h. Third generation Grubbs catalyst (1.123 mg, 0.01540 mmol) in 40 μL dichloromethane was added and after 30 minutes 2 mL ethyl vinylether was added and the mixture was stirred for another 30 minutes. The polymer was purified by precipitation in MeOH, filtered and dried under high vacuum at room temperature to a constant weight to obtain a sticky, slightly brown solid. ^{1}H-NMR ($CDCl_3$): 5.97–5.35 (m, norbornene CH=CH), 4.52 (s, NCH_2CO), 3.80–2.54 (aliphatic side chain and polymer backbone), 2.38–1.89 (aliphatic side chain and polymer backbone), 0.87 (t, CH_3). SEC: M_n = 58.2 kDa, PDI = 1.33.

General procedure for deprotection of the silyl protecting group of P1a, P1b, P2 and P3a to P1a′, P1b′, P2′ and P3a′. A round bottom flask was charged with polymer (800 mg) and THF (20 mL), tetrabutylammonium fluoride (1 M in THF, 4 mL) was added and the mixture was stirred overnight at room temperature under an Ar atmosphere. After the reaction was completed, the solvent was removed *in vacuo*. The polymer was purified by precipitation in MeOH (twice).

P1a′ was obtained as a slightly yellow solid. ^{1}H-NMR ($CDCl_3$): 4.12 (s, broad, CO–O–CH_2), 3.84 (s, broad, CH_2–OH), 3.60 (s, broad, CO–O–CH_3), 2.07–0.76 (m, CH_2, CH_3). SEC: M_n = 18.4 kDa, PDI = 1.10.

P1b′ was obtained as a slightly yellow solid. ^{1}H-NMR: the spectroscopic data were identical to those of **P1a′**. SEC: M_n = 40.8 kDa, PDI = 1.33.

P2′ was obtained as a colourless sticky oil and was purified by a short plug of silica, followed by precipitation in MeOH–H_2O, 15 : 85. ^{1}H-NMR ($CDCl_3$): δ = 4.03 (t, broad, CO–O–CH_2), 3.65 (t, broad, HO–CH_2), 2.38–1.32 (m, CH, CH_2), 0.93 (t, CH_3). SEC: M_n = 38.7 kDa, PDI = 1.96.

P3a′ was obtained as a white solid.[25] ^{1}H-NMR ($CDCl_3$): δ = 7.20–6.24 (m, Ar–H), 4.57 (s, broad, Ar–CH_2), 2.19–1.15 (m, CH_2). SEC: M_n = 18.4 kDa, PDI = 1.08.

General procedure for deprotection of the BOC protecting group of P1c and P3b to P1′ and P3b′. The polymer (200 mg) was dissolved in 10 mL of dry $CHCl_3$, TFA (0.2 mL) was added and the mixture was stirred overnight at room temperature under an Ar atmosphere. The solvent and excess of TFA were removed *in vacuo* using co-evaporation with toluene.

P1c′ was obtained as a slightly yellow solid. ^{1}H-NMR ($CDCl_3$): δ = 7.78 (s, broad, NH_3^+), 3.95 (s, broad, CO–O–CH_2), 3.60 (s, broad, CO–O–CH_3), 3.09 (s, broad, N–CH_2), 2.09–0.79 (m, CH_2, CH_3).

P3c′ was obtained as a white solid.[25] ^{1}H-NMR ($CDCl_3$): δ = 7.85 (s, broad, NH_3^+), 7.45–6.23 (m, Ar–H), 4.98 (s, broad, Ar–CH_2), 3.05 (m, CH_2–NH$_2$), 2.37 (m, CH_2–CO), 2.13–1.10 (m, CH_2).

General procedure for coupling of UPy-synthons 5a/b with free alcohol–amine polymers P1a′–P3b′. A round bottom flask was charged with either 1-(6-isocyanatohexyl)-3-(4-(2-nitrobenzyloxy)-6-tridecyl pyrimidin-2-yl)urea (**5b**) or 1-(6-isocyanatohexyl)-3-(4-methyl-6-((2-nitrobenzyl)oxy)pyrimidin-2-yl) urea (**5a**) (1.05 eq. to number of free alcohols/amines), a drop of dibutyltin dilaurate (DBTDL), $CHCl_3$ (20 mL) and the corresponding polymer (0.100 g). The mixture was refluxed under an Ar atmosphere overnight, whereafter an aminomethylated-polystyrene resin (NovaBioChem, 200–400 mesh) was added and the mixture was stirred for another 3 h. The solution was filtered and the solvent was removed *in vacuo*. The crude polymer was purified by precipitation in methanol.

P5a: ^{1}H-NMR ($CDCl_3$): δ = 9.16 (s, broad, N–H), 8.14 (d, Ar–H), 7.65 (d, 2× Ar–H), 7.51 (m, Ar–H), 7.16 (s, N–H), 6.29 (s, broad, 1H, Ar–H), 5.88 (s, broad, N–H), 5.74 (s, Ar–CH_2–O), 4.26 (s, broad, NH–CO–O–CH_2), 4.12 (s, broad, CO–O–CH_2), 3.60 (s, broad, CO–O–CH_3), 3.33 (m, NH–CH_2, UPy), 3.18 (s, broad, O–CO–NH–CH_2), 2.37 (s, Ar–CH_3), 2.07–0.76 (m, CH_2, CH_3). Conversion alcohols: 47%. SEC: M_n = 24.9 kDa, PDI = 1.12.

P5b: ^{1}H-NMR ($CDCl_3$): δ = 9.16 (s, broad, N–H), 8.11 (d, Ar–H), 7.71 (m, 2× Ar–H), 7.51 (m, Ar–H), 7.09 (s, N–H), 6.25 (s, broad, Ar–H), 5.83 (s, broad, N–H), 5.75 (s, 2H, Ar–CH_2–O), 4.26 (s, broad, NH–CO–O–CH_2), 4.11 (s, broad, CO–O–CH_2), 3.60 (s, broad, CO–O–CH_3), 3.33 (m, NH–CH_2, UPy), 3.18 (s, broad, O–CO–NH–CH_2), 2.58 (s, Ar–CH_2), 2.18–0.79 (m, CH_2, CH_3). Conversion alcohols: 32%. SEC: M_n = 67.9 kDa, PDI = 1.43.

P5c: In the case of **P5c**, no DBTDL was added, instead 50 μL triethylamine was added and the mixture was stirred at room temperature. ^{1}H-NMR ($CDCl_3$): δ = 9.18 (s, broad, N–H), 8.12 (d, Ar–H), 7.66 (m, 2× Ar–H), 7.50 (m, Ar–H), 7.14 (s, N–H), 6.27 (s, Ar–H), 5.73 (s, 2H, Ar–CH_2–O), 4.70 (s, broad, N–H), 3.94 (s, broad, CO–O–CH_2), 3.60 (s, broad, CO–O–CH_3), 3.32 (m, NH–CH_2, UPy), 3.16 (s, broad, NH–CO–NH–CH_2), 2.60 (s, Ar–CH_2), 2.07–0.77 (m, CH_2, CH_3). SEC: M_n = 24.1 kDa, PDI = 1.16.

P6: ^{1}H-NMR ($CDCl_3$): δ = 9.11 (s, broad, N–H), 8.11 (d, Ar–H), 7.63 (m, 2× Ar–H), 7.50 (m, 1× Ar–H), 7.13 (s, N–H), 6.27 (s, Ar–H, UPy), 5.72 (s, Ar–CH_2–O), 4.03 (s, broad, CO–O–CH_2), 3.77 (s, broad, NH–CO–O–CH_2), 3.32 (m, NH–CH_2, UPy), 3.13 (s, broad, O–CO–NH–CH_2), 2.36 (s, Ar–CH_3), 2.34–1.32 (m, CH,

CH_2), 0.91 (t, CH_3). Conversion alcohols: 70%. SEC: M_n = 48.7 kDa, PDI = 1.84.

P7a: ^{1}H-NMR ($CDCl_3$): δ = 9.16 (s, broad, N–*H*), 8.11 (d, Ar–*H*), 7.63 (m, 2× Ar–*H*), 7.58 (m, 1× Ar–*H*), 7.33–6.84 (m, Ar–*H*, styrene), 6.83–6.28 (m, Ar–*H*, styrene), 6.25 (s, Ar–*H*, UPy), 5.71 (s, Ar–CH_2–O), 4.99 (s, broad, Ar–CH_2–O–CO), 4.70 (s, broad, N–*H*), 3.33 (t, NH–CH_2, UPy), 3.17 (t, O–CO–NH–CH_2), 2.57 (t, Ar–CH_2), 2.30 (t, O–CO–CH_2), 2.22–1.09 (m, CH_2, CH_2), 0.87 (t, CH_3). Conversion alcohols: 49%. SEC: M_n = 23.6 kDa, PDI = 1.17.

P7b: In the case of **P7b**, no DBTDL was added, instead 50 μL triethylamine was added and the mixture was stirred at room temperature. ^{1}H-NMR ($CDCl_3$): δ = 9.21 (s, broad, N–*H*), 8.06 (d, Ar–*H*), 7.64 (m, 2× Ar–*H*), 7.47 (m, 1× Ar–*H*), 7.37–6.82 (m, Ar–*H*, styrene), 6.82–6.32 (m, Ar–*H*, styrene), 6.27 (s, Ar–*H*, UPy), 5.68 (s, Ar–CH_2–O), 4.92 (s, broad, Ar–CH_2–O–CO), 4.49 (s, broad, N–*H*), 3.31 (t, NH–CH_2, UPy), 3.09 (t, NH–CH_2, urea), 2.57 (t, Ar–CH_2), 2.30 (t, O–CO–CH_2), 2.22–1.09 (m, CH_2, CH_2), 0.87 (t, CH_3). SEC: M_n = 28.7 kDa, PDI = 1.17.

Coupling of UPy synthon 7 with P4 (P8). A round bottom flask was charged with **P4** (42.0 mg), 6-aminohexyl (6-(3-(4-methyl-6-((2-nitrobenzyl)oxy)pyrimidin-2-yl)ureido)hexyl)carbamate-TFA salt (18.2 eq., 7.20 mg, 0.0109 mmol), triethylamine (10.0 μL) and dry chloroform (4 mL). The mixture was stirred overnight under an argon atmosphere at room temperature. The polymer was purified in MeOH, filtered and dried under high vacuum at room temperature to a constant weight to obtain a sticky, slightly brown solid. ^{1}H-NMR ($CDCl_3$): 9.12 (s, broad, N–*H*), 8.13 (d, Ar–*H*), 7.76–7.57 (m, 1× Ar–*H*), 7.57–7.41 (m, 1× Ar–*H*), 7.14–6.89 (m, 1× Ar–*H*), 6.29 (s, Ar–*H*, UPy), 5.87–5.34 (m, norbornene *CH*=*CH*), 5.68 (s, Ar–CH_2–O), 4.72 (s, broad, Ar–CH_2–O–CO), 4.02 (s, NCH_2CO), 3.52–2.56 (broad, aliphatic side chain and polymer backbone), 2.35 (broad, O–CO–CH_2), 2.32–1.80 (broad, aliphatic side chain and polymer backbone), 1.68–1.40 (broad, aliphatic side chain and polymer backbone), 1.40–1.06 (m, CH_2, CH_2), 1.06–0.67 (m, CH_3). SEC: M_n = 58.2 kDa, PDI = 1.33.

Results and discussion

Design and synthetic strategy

Four types of polymers were selected that differ in backbone rigidity, namely polymethyl methacrylates (series A), poly *n*-butylacrylates (series B), polystyrenes (series C) and polynorbornenes (series D). All polymers comprise pendant self-assembling UPy motifs (Scheme 1). Two different methods to incorporate the self-assembling motif are possible: either *via* direct copolymerization of a UPy-based monomer or *via* post-functionalisation of the polymer with a suitable UPy-based synthon.

In light of a recent report on issues with copolymerizing UPy-based monomers, we opted for the post-functionalization strategy.[14b] Random copolymers with a degree of polymerization (DP) of around 200 and a loading of 10% of post-functionalizable groups were selected. Such DPs are readily attainable *via* a number of controlled polymerization techniques, while a 10% loading of self-assembling groups is a convenient compromise between polymer solubility and a sufficient number of interacting groups. Vinyl-based monomers can be polymerized using controlled radical polymerization techniques,[29–32] wherein excellent control over the molecular weight, the polydispersity index (PDI) and end-groups can be achieved. On the other hand, ring-opening metathesis polymerization (ROMP) using the 3rd generation Grubbs catalyst offers the possibility to produce norbornene based polymers with narrow molecular weight distributions.[33]

To enable post-functionalization, we selected comonomers comprising silyl-protected alcohols, *t*-BOC-protected amines or *N*-succinimide esters. The presence of a protective group in the case of alcohol or amine containing monomers proved to be important to ensure good control during the polymerization reaction.[25] The silyl and *t*-BOC protection groups were selected because they are deprotected under mild conditions. We designed novel *o*-nitrobenzyl protected UPy synthons to react with the pendant alcohol/amine (*via* reaction with isocyanate) or active ester groups (*via* reaction with amine) on the desired polymers (Scheme 2). We selected two different substituents (a: $-CH_3$ and b: $-C_{13}H_{27}$) on the alkylidene-position of the UPy moiety to show the wide applicability of this novel synthon. The CH_3-substituent is the substituent most commonly observed in UPy molecules while the $C_{13}H_{27}$-substituent is expected to enhance the solubility of the synthon.

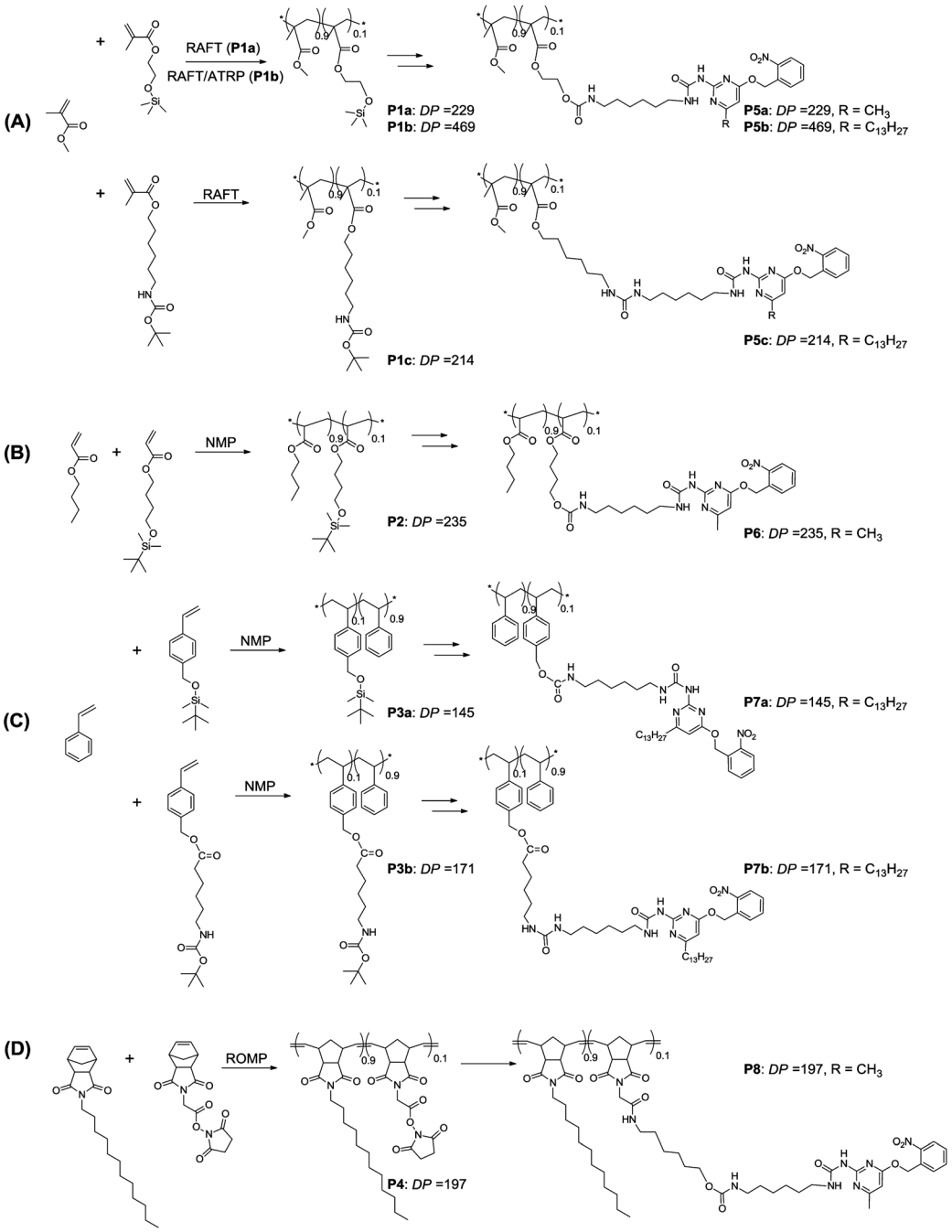
The "caging" of the UPy group is crucial since "free" UPys frequently induce solubility problems, hampering proper characterization of the polymers. In addition, the *o*-nitrobenzyl protective group is UV-labile and conveniently removed upon UV-irradiation.[14,22] In this way, conditions can be selected (*e.g.* in dilute solutions) to induce intramolecular dimerization of the UPy motifs, resulting in folding of individual polymer chains into SCPNs.

In addition to differences in polymer flexibility when keeping the DP constant (**P5a**, **P6**, **P7a** and **P8**), polymers were designed that allow evaluation of the effect of polymer molecular weight on the folding behavior by varying the degree of polymerization (**P5a** and **P5b**). Moreover, the use of a different connectivity (urea *versus* urethane) to attach the UPy group to the polymer (**P5a/c** and **P7a/b**) will provide information on how additional H-bonding interactions affect the folding behavior. Finally, we selected 3 solvents to investigate the ability of all polymers to form SCPNs: chloroform, a weak H-bond donor, tetrahydrofuran (THF), a weak H-bond acceptor and polar dimethylformamide (DMF), a strong H-bond disruptor.

Synthesis of *o*-nitrobenzyl-protected UPy synthons

To graft an *o*-nitrobenzyl protected UPy (phUPy) to the desired amine/alcohol or activated ester pendant prepolymers, we prepared two different phUPy synthons, one comprising an isocyanate group (compound **5**, Scheme 2) and one comprising an amine group (**7**, Scheme 2). The synthesis of phUPy building blocks **5** and **7** is outlined in Scheme 2 and starts from known CDI-activated isocytosines **1a,b** (Scheme 2).[23,24]

The CDI-activated isocytosines **1a,b** were reacted with mono-BOC protected hexyldiamine, to afford UPys **2a,b** in high yield (80–95%). Application of *ortho*-nitrobenzylchloride in

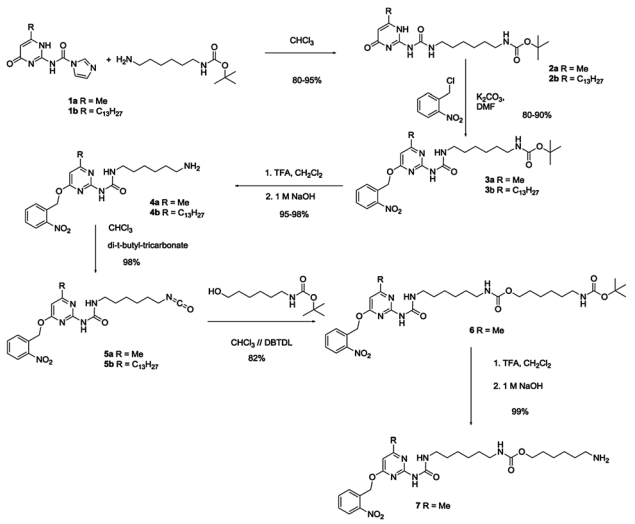


Scheme 1 Synthesis of polymers discussed in this contribution, DP refers to average degree of polymerization.

DMF/K_2CO_3 afforded *O*-alkylation and protected UPys **3a,b** were obtained in excellent yields (80–90%). Removal of the *t*-BOC with trifluoroacetic acid yielded free amines **4a,b**. Reaction of the free amines with di-*tert*-butyltricarbonate[34] afforded isocyanates **5a,b** in near quantitative yield and excellent purity. Finally, isocyanate **5a** was reacted further with *tert*-butyl (6-hydroxyhexyl)carbamate, and after deprotection of the *t*-BOC group, amine **7** was obtained in high yield and purity. Amine **7** incorporating an additional urethane bond was prepared to facilitate comparison between the vinyl polymer series and the norbornene polymer series (Scheme 1).

Synthesis of prepolymers P1–4

Prepolymers based on vinyl-based monomers (series A–C, Scheme 1) were prepared using RAFT,[31] RAFT/ARGET ATRP,[30] or NMP.[32] Polymethyl methacrylate based copolymers **P1a** and **P1c** were prepared using RAFT polymerizations using 4-cyano-4-methyl-5-(phenylthio)-5-thioxopentanoic acid as the chain transfer agent (CTA) under standard conditions for RAFT polymerizations.[35] Two different polymers were prepared: polymer **P1c**, the copolymer of methyl methacrylate with 10 mol% 6-((*tert*-butoxycarbonyl)amino)hexyl methacrylate, providing



Scheme 2 Synthesis of phUPy synthons **5** and **7**.

protected amines on the polymer scaffold and polymer **P1a**, the copolymer of methyl methacrylate with 10 mol% 2-((trimethylsilyl)oxy)ethyl methacrylate (HEMA-TMS), providing protected alcohols on the polymer scaffold. The SEC traces in THF of both polymers showed similar characteristics: $M_n \sim 21$ kDa, with an excellent PDI (1.07) for **P1a** and $M_n \sim 28$ kDa, with PDI = 1.20 for **P1c**. To compare the influence of molecular weight on the self-assembly, we also prepared copolymer **P1b** which like **P1a** contained HEMA-TMS and methyl methacrylate in a 9 : 1 molar ratio but with a molecular weight twice as high as **P1a**. To achieve this, a new controlled polymerization method for obtaining high molecular weight polymers recently reported by Matyjaszewski *et al.* was applied.[36] This method, a combination of RAFT with ARGET ATRP, resulted in a copolymer with a high DP (~470) and a low PDI (1.14).

Polystyrene based polymers were prepared using NMP utilizing *N*-*tert*-butyl-*N*-(2-methyl-1-phenylpropyl)-*O*-(1-phenylethyl) hydroxylamine as the NMP-agent under previously described conditions.[25] Two different polymers were prepared:[25] polymer **P3b**, the copolymer of styrene with 5 mol% 4-vinylbenzyl 6-(*tert*-butoxycarbonylamino)hexanoate and polymer **P3a**, the copolymer of styrene with 12 mol% *tert*-butyldimethyl(4-vinylbenzyloxy) silane. This affords protected amines and alcohols, respectively, on the polymer scaffold (Table 1). The SEC traces of both polymers showed narrow polydispersities ($M_n = 18$ kDa, with PDI = 1.10 for polymer **P3b** and $M_n = 19$ kDa, with PDI = 1.08 for polymer **P3a**).

Using similar polymerisation conditions, poly((*n*-butyl)acrylate) based copolymer **P2** was prepared by copolymerizing *n*-butylacrylate with 10 mol% 4-((*tert*-butyldimethylsilyl)oxy)butyl acrylate using *N*-*tert*-butyl-*N*-(2-methyl-1-phenylpropyl)-*O*-(1-phenylethyl)hydroxylamine as the NMP-agent. A copolymer with a molecular weight of 35 kDa and a DP of ~235 was obtained. This copolymer showed a larger PDI (~1.8, Table 1) than its styrene counterpart.

Polynorbornene based copolymer **P4** was prepared *via* ring-opening metathesis polymerisation of (*N*-dodecyl)-5-norbornene-*exo*-2,3-dicarboximide with (*N*-acetyloxy-2,5-pyrrolidinedione)-5-norbornene-*exo*-2,3-dicarboximide in a molar ratio of 9 : 1, using a third generation Grubbs catalyst.[28] A polymer with a molecular weight M_n of 58 kDa and a decent PDI (1.33) was obtained.

All prepolymers **P1–P4** were characterised by SEC and ^{1}H-NMR, the results are summarised in Table 1. In all cases, the observed polymer composition matches very well with the composition of the feed.

Synthesis of phUPy containing polymers P5–P8

Polymers **P1–P3** were deprotected using either trifluoroacetic acid (**P1c** and **P3b**) to yield the corresponding free amines or tetrabutylammonium fluoride (TBAF) (**P1a,b**, **P2** and **P3a**) to yield the corresponding free alcohols. Subsequently, phUPy building blocks **5a** and **5b** were coupled (see Scheme 2 for details) to the free alcohol and free amine containing polymers, affording polymers **P5–P7**. Reaction of the isocyanates to the free amines was quantitative, while reaction with the free alcohols proceeded with conversions of 32–70%. The activated NHS-ester in **P4** was reacted with phUPy **7**, affording polymer **P8** in quantitative yield. PhUPy building blocks and polymers **P5–P8** were fully characterised with SEC (Fig. S1–S7†), DLS (Fig. S8–S14†), ^{1}H-NMR (Fig. S15–S19†) and infrared spectroscopy (Fig. S20–S24†). The relevant data are summarised in Table 2. As an example, the ^{1}H-NMR of **P7b** in $CDCl_3$ is shown in Fig. 2. The spectrum shows the presence of the phUPy-moiety (peaks a–g), while comparison of the integrals of peaks m with i, j and s indicates a quantitative reaction of the amines of prepolymer **P3b**.

Table 1 Results of the analysis of prepolymers **P1–P4** by ^{1}H-NMR and SEC[a]

Series	Polymer	Method	Feed ratio (m_A/m_B)	m_A	Conversion (%)	Observed ratio (m_A/m_B)	$M_{n,th}$[b] (Da)	DP_{th}[b]	$M_{n,exp}$[c] (Da)	PDI[c]
A	**P1a**	RAFT	90/10	MMA	80	90/10	25 200	229	21 200	1.07
A	**P1b**	ATRP/RAFT	90/10	MMA	59	89/11	51 800	469	59 400	1.14
A	**P1c**	RAFT	90/10	MMA	72	92/8	22 800	214	28 000	1.20
B	**P2**	NMP	91/9	*n*BA	93	91/9	33 400	235	34 800	1.83
C	**P3a**	NMP	91/9	St	63	88/12	15 900	145	19 000	1.08
C	**P3b**	NMP	95/5	St	74	95/5	20 200	171	18 100	1.10
D	**P4**	ROMP	90/10	Norb.	>99	93/7	65 200	197	58 200	1.33

[a] Conversions and observed incorporation of the two monomers m_A and functional monomer m_B as determined by ^{1}H-NMR. [b] Based on conversion. [c] All SEC-measurements were carried out on a THF system using a polystyrene calibration, after precipitation of the polymer.

Table 2 Overview of UPy containing polymers **P5a–P8**

Series	Polymer	Prepolymer	Obs. ratio (m_A/m_B)[a]	DP_{th}[a]	# UPys[c]	$M_{n,exp}$[b] (Da)	PDI[b]
A	**P5a**	**P1a**	90/10	229	11	24 900	1.12
A	**P5b**	**P1b**	89/11	469	17	67 900	1.43
A	**P5c**	**P1c**	92/8	214	17	24 100	1.16
B	**P6**	**P2**	91/9	235	15	48 700	1.84
C	**P7a**	**P3a**	88/12	145	9	23 600	1.17
C	**P7b**	**P3b**	95/5	171	9	28 700	1.17
D	**P8**	**P4**	93/7	197	14	57 000	1.26

[a] Calculation based on corresponding prepolymers. [b] All SEC-measurements were carried out on a THF system using a polystyrene calibration after isolation of the polymer. [c] Calculation based on conversion of alcohols/amines/activated ester.

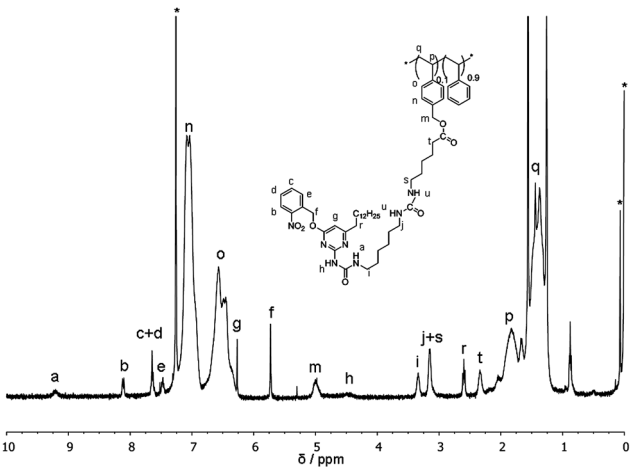


Fig. 2 ^{1}H-NMR of **P7b** in $CDCl_3$.

Thus, the influence of the nature of the backbone on the polymer folding behavior can be evaluated by comparing representatives of the 4 different series, **P5a**, **P6**, **P7** and **P8**, all showing similar DPs. In addition, by comparing **P5a** (DP = 230) with **P5b** (DP = 460), the influence of molecular weight on the polymer folding behavior can be assessed. Finally, the influence of the linker group (urea or urethane) can be evaluated for series A (flexible polymer, **P5a** and **P5c**) and series C (more rigid polymer, **P7a** and **P7b**).

Influence of polymer stiffness and solvent on intramolecular UPy dimerization

We previously reported that UPy moieties attached to a polymer can dimerize intramolecularly under sufficiently dilute conditions.[14] The formation of the hydrogen bonds restricts the conformational freedom of the polymer chain and results in a chain collapse. This collapse was conveniently probed by SEC and AFM. Here, we induced deprotection of the protected UPys by illuminating a solution of the desired polymer (c = 1 mg mL^{-1}) with UV light (UV-A, λ_{max} = 350 nm) in a Luzchem photoreactor for 2 hours. We apply a combination of different techniques to assess the effect of *o*-nitrobenzyl deprotection. First, ^{1}H-NMR provides information on the ability of the UPy groups to dimerize after deprotection. Size exclusion chromatography (SEC) and dynamic light scattering (DLS) were used to evaluate the size of the polymers before and after deprotection and quantify the degree of chain collapse and single chain character. Finally, we used atom force microscopy to visualise the single chain character of the formed SCPNs. All techniques were performed in three different solvents: chloroform, DMF and THF. Although solvent–polymer backbone interaction parameters are important variables, this study shows that the main solvent dependences here are related to the interaction of the supramolecular unit and the solvent (*vide infra*). In fact, the second virial coefficients for all polymer systems investigated here are similar for both THF and chloroform (5–9 × 10^{-4} mol cm^3 g^{-2}).[37] In chloroform, UPys with an aliphatic substituent on the pyrimidinone ring usually dimerize *via* strong four-fold hydrogen bonds *via* the 4[1*H*]-pyrimidinone dimer.[21b] In more polar solvents UPy-dimerisation is weaker, as is evidenced by the presence of a large percentage of the weaker pyrimindin-4-ol dimer (THF) or its complete absence (DMSO/DMF).[38] In all cases, the polymer solutions were evaluated before and after illumination with UV light. First, we discuss in detail the results of these studies on polymethacrylate **P5a**.

Fig. 3 shows the ^{1}H-NMR spectrum of **P5a** dissolved in $CHCl_3$ (c = 2 mg mL^{-1}) before and after deprotection. Before

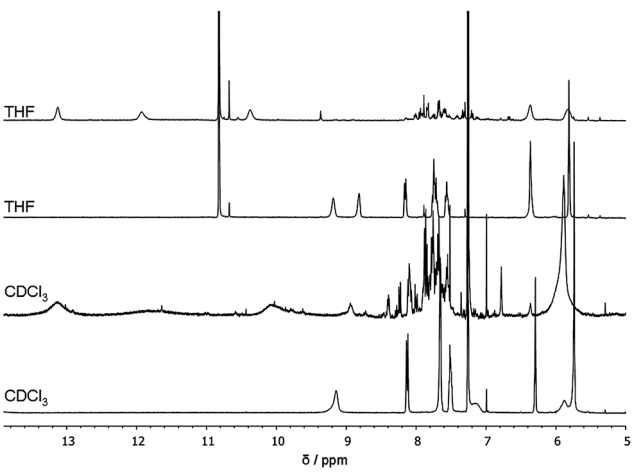


Fig. 3 ^{1}H-NMR spectra of **P5a** in $CDCl_3$ before (bottom) and after (second from bottom) deprotection and in THF-d_8 before (second from top) and after (top) deprotection. The peak at 10.8 ppm in THF-d_8 corresponds to an impurity in the deuterated solvent.

deprotection, the intramolecular H-bonded proton of the urea of the phUPy is clearly visible at 9.2 ppm, while no other H-bonded protons are visible. After deprotection three additional signals appeared around 10.3, 11.9 and 13.1 ppm. These are attributed to the UPy dimer in its 4[1*H*]-pyrimidinone tautomer. Compared to the "free" UPy dimer in $CDCl_3$, the signals are significantly broadened, indicative of a reduced mobility of the UPy dimer. The latter is in line with our expectations for UPy dimers in a SCPN. In THF-d8, a similar pattern is observed before and after deprotection of the UPy group, indicating that also in this rather polar solvent at rather low concentrations 4[1*H*]-pyrimidinone dimers are formed. Remarkably the NH peaks are much sharper compared to those in THF. These results indicate that in THF the UPys are able to dimerize into the strong 4[1*H*]-pyrimidinone dimer when attached to a polymer chain and that the high local concentration of UPys inside a polymer chain helps dimerization into a 4[1*H*]-pyrimidinone dimer. In DMF-d_7 after deprotection (Fig. S16†), two signals at 11.8 ppm and 9.3 ppm suggest the presence of the 6[1*H*]-pyrimidinone monomer (Fig. S16†),[38] while smaller subsets at 13.0 and 10.3 ppm suggest the presence of a 4[1*H*]-pyrimidinone dimer.[38]

SEC gives qualitative information on the coil to globule transition in polymers because it probes the hydrodynamic volume of macromolecules. In our previous work, we observed that removal of the protecting group results in an increase of the SEC retention time, indicating a reduction of the hydrodynamic volume of the polymer chain. However, since the measurements are typically conducted relative to a standard and interactions of the polymer with the column may occur, the results are not always straightforward to interpret. In contrast, dynamic light scattering gives a direct way of determining the size of the polymers in solution provided that intermolecular aggregation can be suppressed.

We performed SEC and DLS measurements on solutions of **P5a** in THF ($c = 1$ mg mL^{-1}) before and after deprotection of the UPy group. The SEC traces of **P5a** at 1 mg mL^{-1} in THF before and after deprotection are shown in Fig. 4. A clear increase in the retention time from 14.3 ($M_n = 24.9$ kDa, PDI = 1.12) to 14.6 min ($M_n = 20.3$ kDa, PDI = 1.17) is observed, corresponding to a 19% decrease in apparent molecular weight. Since ^{1}H-NMR clearly shows the formation of UPy dimers under these conditions, this is consistent with a collapse of the polymer chain as a result of H-bond formation. This reduction in apparent molecular weight is in good agreement with earlier reported, UPy based nanoparticles.[14]

To assess if the UPy dimerization is indeed an intramolecular process, DLS measurements were performed on solutions of **P5a** before and after deprotection in THF (Fig. 4). From the intensity distributions, the hydrodynamic radius (R_h) was determined. The R_h stayed constant at 5.0 nm, indicating that the UPy dimerization is indeed an intramolecular process; the lack of significant change in R_h can be explained by the small size of the particle, making small differences hard to detect. These combined results allow us to conclude that particles of nanometer-sized dimensions and containing one polymer chain only are formed in a relatively polar solvent like THF. SEC in DMF reveals only small changes for **P5a** and an almost negligible collapse of 2% is observed (Table S1†).

In chloroform, the behaviour of **P5a** is strikingly different, as was already indicated by the broader signals of the 4[1*H*]-pyrimidinone dimer in ^{1}H-NMR (*vide supra*). SEC in $CHCl_3$ ($c = 1$ mg mL^{-1}) shows that $M_n = 14.3$ kDa and PDI = 1.33 before deprotection (Fig. 5). After deprotection, an *increase* in the apparent molecular weight is observed to $M_n = 18.1$ kDa, PDI = 1.24. The lower molecular weight observed in $CHCl_3$ compared to THF before deprotection could indicate that **P5a** has more interactions with the column, which results in an increase in the retention time. In DLS, in contrast, a decrease in R_h (Fig. 5) can be observed from 7.1 to 6.6 nm after deprotection, but the polydisperse peaks observed before and after deprotection indicate a significant degree of interparticle interactions. While an apolar solvent like chloroform enables strong UPy dimerization, interparticle interactions are more pronounced than in the more polar solvent THF. These results indicate that solvent is an important parameter in the formation of well-defined SCPNs starting from **P5a**.

The ability of the UPy group to dimerize after deprotection in polybutylacrylate-based **P6**, polystyrene-based **P7a** and polynorbornene-based **P8** polymers is quite comparable to that of **P5a**, as evidenced by ^{1}H-NMR. Spectra for deprotected polymers are shown in Fig. S16–S19;† clear formation of the 4[1*H*]-pyrimidinone dimer in THF and $CHCl_3$ can be observed. This allows us to conclude that backbone rigidity does not have a significant influence on the ability of the polymers to form UPy dimers.

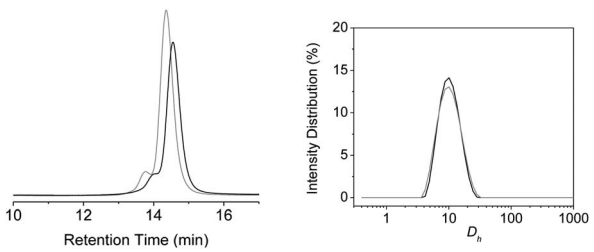


Fig. 4 SEC measurements on polymer **P5a** in THF (left) and intensity distribution *versus* hydrodynamic diameter (D_h) from DLS measurements on polymer **P5a** in THF (right), before (grey) and after deprotection (black) of the photocleavable group.

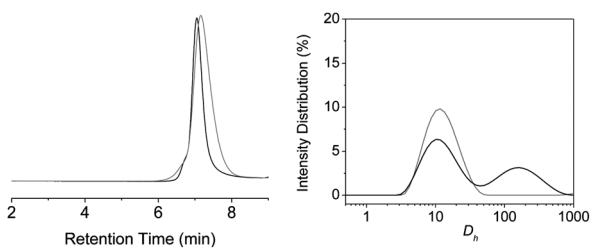


Fig. 5 SEC measurements on polymer **P5a** in $CHCl_3$ (left) and intensity distribution *versus* hydrodynamic diameter (D_h) from DLS measurements on polymer **P5a** in $CHCl_3$ (right), before (grey) and after deprotection (black) of the photocleavable group.

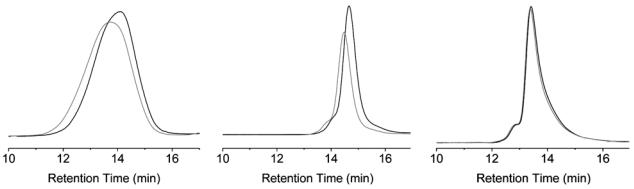


Fig. 6 SEC measurements on polymer **P6** in THF (left), **P7a** in THF (middle) and **P8** in THF (right), before (grey) and after deprotection (black) of the photocleavable group.

SEC-measurements in THF show a substantial decrease in apparent molecular weight (Fig. 6, full data in Table 3) for **P6**, **P7a** and **P8** (20% for **P6**, 19% for **P7a** and 8% for **P8**) after deprotection of the photolabile nitrobenzyl group, indicative of a collapse of the polymer chains upon UPy dimerization. In addition, DLS measurements in THF indicate a decrease of the R_h. For example, the R_h of **P8** decreases from 7.3 nm to 6.3 nm, while it decreases for **P7a** from 4.8 nm to 4.4 nm (Fig. S14 and S12†). Although a small *increase* in R_h is observed for **P6**, it is accompanied by a decrease in the presence of larger aggregates (Fig. S11†), indicating a better defined system. The difference with the SEC-measurements in this latter observation can be rationalized since the shear-forces involved in SEC-measurements probably disrupt the weak interchain interactions in such a polar solvent. In DMF, we also see small decreases in R_h in DLS and apparent hydrodynamic volume in SEC for **P7a** (Table S1, Fig. S5 and S12,† a change of 32% in SEC and a decrease in R_h from 4.6 to 4.4 nm in DLS after deprotection). Due to a poor match in refractive index difference for **P6**, and **P8** with DMF, DLS and SEC were not possible.

In chloroform we also observe a similar behaviour for urethane containing polymers **P6**, **P7a** and **P8** to that for **P5a**. In SEC measurements, the polymers show large polydispersities before and after deprotection of the photolabile group and activation of the hydrogen bonds, and also show large decreases in apparent hydrodynamic volume (changes from 47–77%, Table 3), indicating that also **P6**, **P7a** and **P8** show relevant interparticle interactions in chloroform.

This behaviour is also observed in DLS measurements for **P6** (Fig. S11†), where also aggregates are visible before and after deprotection of the photolabile protecting group. Surprisingly, for the stiffer backbones, polystyrene-based **P7a** and polynorbornene-based **P8**, a collapse can be observed in DLS after deprotection and relative narrow distributions are obtained (Fig. S12 and S14†). From these experiments we conclude that the exact nature of the polymeric backbone is not the most important parameter in the formation of well-defined SCPNs but that the choice of solvent is a far more important parameter. First, the polymer has to be well-soluble in the chosen solvent, second, the solvent must allow for a substantial amount of H-bonding inside the particle and third, interparticle interactions have to be suppressed. A possible explanation for the ability of THF to suppress the interparticle interactions can be that THF, a H-bond acceptor, is in competition with interparticle interactions, thus limiting the formation of large aggregates.

Influence of M_n on the formation of SCPNs

The influence of molecular weight on the folding behaviour was investigated by comparing polymethacrylate based **P5a** (DP = 230) with its heavier analogue **P5b** (DP = 470). Although **P5b** is twice as large as **P5a**, it has a quite comparable number of phUPys. The behaviour of both polymers is quite similar, although the larger size of **P5b** makes interpretation of the data more straightforward. In THF the apparent hydrodynamic volume of **P5b** decreases with 12% (Table 3 and Fig. S2†) in SEC measurements while also a significant decrease in R_h can be

Table 4 DLS results of folding experiments on polymers **P5–P8**[a]

Solvent	THF		$CHCl_3$	
Polymer	$R_{h,p}$ (nm)	$R_{h,d}$ (nm)	$R_{h,p}$ (nm)	$R_{h,d}$ (nm)
P5a	5.0	5.0	7.1	6.6
P5b	12.6	11.8	15.3	18.1
P5c	nd	nd	62.5	52.1
P6	9.3	9.9	8.2	16.5
P7a	4.8	4.4	5.4	5.2
P7b	6.3	5.7	6.4	5.5
P8	7.3	6.3	9.9	9.0

[a] nd = not determined.

Table 3 SEC results of folding experiments on polymers **P5–P8**[a]

Solvent		THF					$CHCl_3$				
Polymer	Backbone	$M_{n,p}$	PDI_p	$M_{n,d}$	PDI_d	Collapse (%)	$M_{n,p}$	PDI_p	$M_{n,d}$	PDI_d	Collapse (%)
P5a	Methacrylate	24 900	1.12	20 300	1.17	18.6	14 300	1.33	18 100	1.24	−27.1
P5b	Methacrylate	67 900	1.43	60 100	1.46	11.5	366 000	2.58	86 100	2.54	76.5
P5c	Methacrylate	24 100	1.16	21 500	1.19	10.6	254 300	2.54	167 200	2.94	34.3
P6	Acrylate	48 700	1.84	39 100	1.65	19.8	465 800	2.90	107 200	6.14	77.0
P7a	Styrene	23 600	1.17	19 100	1.18	18.9	59 400	2.72	20 200	1.63	66.1
P7b	Styrene	28 700	1.17	23 300	1.22	18.8	19 200	4.96	14 400	1.59	25.1
P8	Norbornene	57 000	1.26	52 500	1.42	8.0	101 800	1.81	54 500	1.55	46.5

[a] $M_{n,p} = M_n$ photoprotected polymer in Da. $M_{n,d} = M_n$ deprotected polymer in Da; M_n relative to PS standards.

observed from 12.6 nm to 11.8 nm after deprotection (Table 4 and Fig. S9†). A similar behaviour is visible in DMF; an apparent decrease in hydrodynamic volume of 20% in SEC and a significant decrease in R_h from 9.1 nm to 8.5 nm in DLS after deprotection (Table S1 and Fig. S2 and S9†). Also in chloroform the behaviour of **P5b** is similar to that of **P5a**; very broad peaks are observed in SEC, while also broad distributions are visible in DLS (Tables 3 and 4 and Fig. S2 and S9†), again indicating that interparticle interactions are present. These results allow us to conclude that increasing the polymer length does not influence the ability of the polymer to form a SCPN.

Influence of linker unit on the formation of SCPNs

To investigate the influence of the linker unit between the UPy and the polymer backbone on the folding we compared urethane containing polymethacrylate-based **P5a** and polystyrene-based **P7a** with their urea containing counterparts **P5c** and **P7b**, respectively. Polymers **P5c** and **P7b** have comparable M_n, PDI and number of phUPys as their urethane counterparts (Table 2). Polymer **P5c** shows a similar collapse in THF-SEC to **P5a** (19% *versus* 12%, Table 3), and a clear decrease in R_h can be observed from the DLS measurements (Table 4). Also in $CHCl_3$ the behaviour is similar for **P5c** to that for **P5a**; polydisperse aggregates can be observed in both SEC and DLS measurements (Tables 3 and 4 and Fig. S3 and S10†).

The comparison of **P7a** with **P7b** shows similar results. In THF, **P7b** collapses into a smaller particle after deprotection as is evidenced by SEC (Table 3 and Fig. S6†) and DLS measurements (Table 4 and Fig. S13†), while in SEC measurements in chloroform (Table 3 and Fig. S6†) large aggregates are present, although the DLS measurements show a collapse in DLS with relative narrow distributions (Fig. S13†). These results allow us to conclude that the *linker* between the polymeric backbone and the UPy does not significantly influence the ability to form SCPNs.

Atomic force microscopy

AFM is a widely used technique to study nanoparticles; to visualize the nanoparticles obtained in this study we selected two polymers differing in polymer flexibility. Polymethacrylate based **P5c** has a relatively flexible backbone, while polystyrene based **P7b** has a relatively stiff backbone. Dilute solutions ($c = 10^{-4}$ mg mL^{-1}, Fig. 7) of deprotected nanoparticles in dioxane were dropcast on a freshly cleaved mica-surface and the resulting nanoparticles were measured. Dioxane was chosen as a solvent that resembles THF in terms of chemical nature and polarity but evaporates slower, thus decreasing potential dewetting phenomena.[26]

The AFM micrographs show comparable features for both polymers; representative height images are shown in Fig. 7. The micrographs show spherical particles, no large, undefined aggregates are visible. As expected, some polydispersity is present in the size of the particles for both polymers. The nanoparticles are on average 25–30 nm in diameter, which is in good agreement with earlier reported sizes for UPy-based nanoparticles.[14]

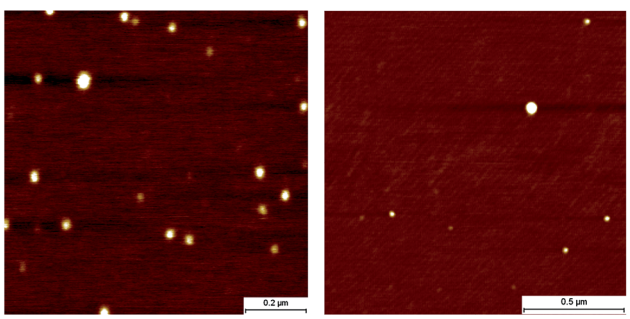


Fig. 7 AFM height-micrographs of polymers **P5c** (left) and **P7b** (right).

Conclusions

In conclusion, we have shown that a modular post-functionalization approach is an efficient way to produce a large library of polymers capable of forming SCPNs. Using dynamic light scattering (DLS) and size exclusion chromatography (SEC) techniques the change in hydrodynamic radius of these particles upon removal of the photoprotecting group has been shown. ^{1}H-NMR showed the dimerisation of the UPy-moieties. Last, in atomic force microscopy (AFM) studies, the appearance of well-defined particles after formation of the H-bonds is visualised. Interestingly, neither the difference in backbone rigidity or the molecular weight nor the linking moiety between the different polymeric backbones results in notable differences in the formation of the SCPNs. Solvent is however a crucial parameter in the formation of well-defined SCPNs. Well-defined SCPNs are formed in solvents that show some competition for H-bonding (THF), and particles with a 8–20% lower hydrodynamic volume than the protected polymers are observed. These particles form no networks even though a large number of UPy-groups are available. In less competitive solvents (*e.g.* $CHCl_3$), the tendency to form defined particles is less pronounced and more interparticle interactions are observed in DLS and SEC. This illustrates the versatility and freedom of choice in selecting polymeric backbones when SCPNs for advanced applications like catalysis and sensing are pursued.

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