Automated Large-Scale Synthesis of Supramolecular Oligo(*p*-benzamide) Block Copolymers

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ABSTRACT: A fully automated large-scale synthesis procedure has been developed that allows the preparation of supramolecular rod−coil copolymers on a 100 g scale. The new reaction cycle allows the stepwise growth of oligo(*p*-benzamide)s onto the chain end of amine-terminated polymers. Amine-terminated poly(ethylene glycol) (PEG, $M_n = 5000$ g mol^{-1}) and poly(styrene) (PS, $M_n = 2950$ g mol^{-1}) were prepared, and an octa(*p*-benzamide) oligomer block was grown from the chain end in an automated computer-controlled reaction cycle. Plotting the apparent molecular weight of the PEG copolymer against the number of reaction cycles revealed a linear relationship, which emphasized the high level of control this method offers. The block copolymers show strong aggregation in nonpolar solvents such as chloroform. Remarkably, transmission electron microscopy images of drop-cast chloroform solutions show perfectly uniform rodlike micelles for the PEG and the PS copolymer.

Introduction

Rod−coil copolymers in which the rod block consists of a strongly aggregating oligomer that drives the self-assembly process have received significant attention over the past decade.[1] Because of the small dimensions of the oligomeric rod block, solution or solid state structures can be obtained with such systems on length scales much smaller than typically obtainable by coil−coil copolymers.[2] Most examples of oligomeric rod−coil copolymers described so far rely on nonspecific π-interactions to obtain higher degrees of order in solution or the solid state. In a few examples, however, directional hydrogen bonds are exploited to induce order into the block copolymer. β-sheet-forming oligopeptides have, for example, been attached to coil-type polymers by several groups.[3−7] The peptide motif dominated the superstructure formation as long sheets of oligomers; i.e., rodlike micelles were observed in solution.

Our group has been investigating copolymers of the β-sheet mimicking oligo(*p*-benzamide) (OPBA). We have developed several synthetic routes in solution as well as on solid support and described the aggregation phenomena in detail.[8−13]

All of the above-mentioned block copolymers consist of a precisely defined oligomeric block that was synthesized on solid support or using standard organic synthesis procedures often involving laborious protection chemistry. Therefore, the amounts of product available for these very precisely defined materials are typically limited to the multi-milligram regime. In recent years, many groups have synthesized ever more complex and precisely defined polymeric materials using the tools of classical organic chemistry.[14] While this approach provides a high level of structural confidence, multistep organic syntheses can severely hamper the preparation of larger quantities of materials. In order to be able to evaluate materials properties especially in the bulk, synthetic routes are required that give access to the 10−100 g scale without the need for laborious multistep syntheses and wasteful purification procedures.

We therefore devised a new synthetic procedure that is fully automated, can be run on the 100 g scale, yet produces surprisingly well-defined supramolecular OPBA rod−coil copolymers.

Here we report the proof of concept using two different types of coil polymers (PS and PEG) onto which we condensed octa(*p*-benzamide)s in an automated computer-controlled fashion.

Experimental Section

Instrumentation. ^{1}H and ^{13}C nuclear magnetic resonance spectra (NMR) were recorded at a frequency of 300 MHz on a Bruker AC 300 or on a Bruker AMX 400 working at 400 and 100 MHz, respectively, for ^{13}C (on the Bruker AMX 400), using benzene-d_6 as solvent. ^{29}Si NMR spectra were recorded on a Bruker AMX 400 at 79.49 MHz which was referenced externally to TMS. Size exclusion chromatography in tetrahydrofuran (THF) or chloroform was performed on an instrument consisting of a Waters 717 plus autosampler, a TSP Spectra Series P 100 pump, and a set of three PSS−SDV 5 μm columns with 100, 1.000, and 10.000 Å porosity. Calibration was carried out using poly(styrene) standards provided by Polymer Standards Service and performing a third-order polynomial fit. The eluent was used at 30 °C and at a flow rate of 1 mL min^{-1}. UV absorption was detected by a SpectraSYSTEM UV2000. The specific refractive index increment (d*n*/d*c*) was measured at 30 °C on an Optilab DSP interferometric refractometer (also RI detector). For measurements in dimethylformamide (DMF) containing 1 g L^{-1} of lithium bromide, an Agilent 1100 Series GPC-Setup (gel permeation chromatography) was used as an integrated instrument including a PSS HEMA column ($10^6/10^5/10^4$ g mol^{-1}), a UV (254 nm), and RI detector. Calibration was carried out using polystyrene standards provided by Polymer Standards Service. The eluent was used at 50 °C and at a flow rate of 1 mL min^{-1}. Field desorption mass spectra were measured on a Finnigan MAT 95. A Philips EM 420 transmission electron microscope using a LaB_6 cathode at an acceleration voltage of 120 kV was used to obtain TEM images. TEM grids (carbon film on copper, 300 mesh) were obtained from Electron Microscopy Sciences, Hatfield, PA. UV/vis spectra were measured on a Perkin-Elmer Lambda 2.

Materials. Cyclohexane (Acros, p.A.) and tetrahydrofuran (THF) (Acros, p.A.) for polymerizations were purified by cryo-transfer from a dark-red living polystyrene (PS, 99%), solution just prior to use. Styrene (Acros) was stored over CaH_2 (Fluka, 99%) until used. Allylamine (Acros, 99%) was used as received. *sec*-Butyllithium (1.6 M, Acros) was used as received. The concentration of the initiator was determined by the Gilman double titration

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method.[15] Chlorodimethylsilane (Acros, 99%) was dried over CaH_2 and cryo-transferred into an ampule until used. CaH_2 was purchased from Fluka and used as received. Toluene (extra dry, with molecular sieves, water <50 ppm) was purchased from Acros and used without further purification. Karstedt's catalyst in xylene (2.1−2.4% Pt) was purchased from ABCR GmbH & Co. KG and used as received. All degassing and cryo-transfer procedures were carried out using liquid nitrogen as cooling agent if not otherwise mentioned. *N*-Methyl-2-pyrrolidonone (NMP) (Acros, p.A.) and pyridine (Acros, p.A.) were dried over CaH_2. 4-Aminobezoic acid (Acros, 99%), thionyl chloride (Acros, 99%), and palladium on char coal (Acros, 10% Pd on C) were used as received. Deuterated chloroform-*d* (99.8%), DMSO-d_6 (99.8%), DMF-d_7 (99.5%), and pyridine-d_5 (99.5%) were purchased from Deutero GmbH and used as received.

General Procedure on Synthesis of Oligo(*p*-benzamide)s (OPBA) onto Aniline or Monofunctionalized Amine-Terminated Polymer. The given amount of aniline or polymer was dissolved and heated to the specified temperature. One equivalent monomer (**1**) (dissolved in THF) or water (dissolved in THF) was added alternating after the particular time interval. After the reaction cycles the reaction mixture was poured into ether (−30 °C), filtered, and dried.

4-*N*-Sulfinylaminobenzoyl Chloride (1). 4-Aminobenzoic acid (20.18 g, 0.147 mol) and thionyl chloride (50 mL, 0.69 mol) were refluxed until all starting material was dissolved (2 h). Excess thionyl chloride was removed by distillation. The product was obtained as a yellow solid after vacuum distillation (2×10^{-2} mbar; 130 °C). Yield: 27.12 g (0.134 mol; 91%). ^{1}H NMR (300 MHz, pyridine-d_5) δ [ppm]: 7.78 (d, J = 8.7 Hz, 2 H, ar, C3-*H*, C5-*H*); 8.09 (d, J = 8.7 Hz, 2 H, ar, C2-*H*, C6-*H*).

MPEG-Ar$_1$-NO$_2$ (2). Monomethyl poly(ethylene glycol)$_{5K}$ (150 g, 30 mmol) (MPEG) and pyridine (15 mL) were dissolved in dichloromethane (600 mL), and 4-nitrobenzoyl chloride (28 g, 151 mmol) was added. The mixture was refluxed for 2 days followed by stirring at r.t. for one more day. After removing most of the solvent, the mixture was precipitated in the 10-fold amount of diethyl ether. The white solid was recovered by filtration, washed with diethyl ether, and dried in vacuum at 40 °C. Since the product still contained trace amounts of pyridine and 4-nitrobenzoyl chloride, it was reprecipitated from dichloromethane into diethyl ether. Yield: 150 g (29.12 mmol; 97%). ^{1}H NMR (300 MHz, DMSO-d_6) δ [ppm]: 8.19 (d, J = 8.8 Hz, 2 H ar, C3-*H*, C5-*H*); 8.35 (d, J = 8.81 Hz, 2 H ar, C2-*H*, C6-*H*).

MPEG-Ar$_1$-NH$_2$ (3). 2 (150 g) and ammonium formate (170 g, 2.7 mol) were dissolved in methanol (1 L) and dichloromethane (200 mL). Palladium on charcoal (3 g, 10%) was added under a nitrogen atmosphere, and the resulting mixture was stirred at r.t. for 12 h. After filtration through Celite the solvent was removed by vacuum distillation. The residue was dissolved in chloroform and washed with water. The organic phase was dried over magnesium sulfate, and most of the solvent was removed in vacuum. The resulting mixture was precipitated in the 10-fold amount of diethyl ether, recovered by filtration, and dried in vacuum at 40 °C. Yield: 121 g (24 mmol, 83%). ^{1}H NMR (300 MHz, DMSO-d_6) δ [ppm]: 5.95 (s, J = 8.8 Hz, 2 H, −NH_2); 6.54 (d, J = 8.8 Hz, 2 H ar, C3-*H*, C5-*H*); 7.62 (d, 8.8 Hz, 2 H ar, C2-*H*, C6-*H*).

Anionic Polymerization. A typical polymerization is as follows: The polymerizations were conducted in vacuo using a 1 L glass reactor, containing a 100 mL flask with living polystyrene solution in cyclohexane (closed by a separate Teflon tap), a magnetic glass stirrer, a Teflon septum, and an additional Teflon tap to remove the reactor from the vacuum line. The reactor was connected to a vacuum line (with standard oil pump ca. 10^{-2} mbar) containing a graduated ampule and the flasks with solvents and reagents. It was evacuated, removed from the line, and rinsed with the living polystyrene solution. Using cryo-transfer procedures, the living PS solution was transferred back into the 100 mL flask with any other impurities. The reactor was again connected to the vacuum line and evacuated for another hour. The monomer was cryo-transferred to the ampule (ca. 20 mL) and then transferred to the reactor. Finally, cyclohexane was transferred into the reactor (concentration of monomer ∼10 vol %). The frozen solution was degassed by one further freeze−thaw cycle.

The reaction mixture was allowed to warm to −5 °C and was then initiated with the appropriate amount of *sec*-BuLi using a gastight syringe closed by a valve (Hamilton). After stirring for 10 min at −5 °C, the mixture was heated to 40 °C for further 10 h to complete the reaction. Quenching of the living chains was established by cryo-transfer of chlorodimethylsilane into the reactor until the deep red color of the living anions vanished. Data for PS-SiMe$_2$H: ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]: 0.1 (s, Si-(CH_3)$_2$), 0.65−2.29 (m, *sec*-Bu (initiator), *CH*CH_2(Ph)), 3,87 (m, Si−*H*), 6.5−7.2 (m, CHCH$_2$(*Ph*)). ^{29}Si{^{1}H} NMR (79.43 MHz, $CDCl_3$) δ [ppm]: −7.5 (s, *Si*Me$_2$H). GPC: M_n = 2900 g mol^{-1}, M_w = 3200 g mol^{-1}, PDI = 1.08 (UV detection).

PS-SiMe$_2$(CH$_2$)$_3$NH$_2$ (4). PS-SiMe$_2$H (6 g) was dissolved in dry toluene (ca. 10 mL), and a 4-fold excess of allylamine was added with a syringe. Hydrosilylation was started by adding Karstedt's catalyst in xylene (50 μL) to the solution at room temperature. The reaction was completed after 8−10 days stirring at r.t. (control over completion via IR). ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]: −0.17 (m, Si*Me*$_2$, 6H), 0.34 (br, Si*CH*$_2$, 2H), 0.69 (t, br, *CH*$_3$, 6H (initiator)), 1.2−2.3 (br, C*H*$_2$*CH*(Ph)), 5.4 (m, C*H*═C*H*, 2H), 6.4−7.2 (br, CH$_2$CH(*Ph*)). ^{29}Si{^{1}H} NMR (79.43 MHz, $CDCl_3$) δ [ppm]: 4.3 (s, *Si*Me$_2$). GPC: M_n = 2950 g mol^{-1}, M_w = 3130 g mol^{-1}, PDI = 1.06 (UV detection).

Synthesis of PEG-OPBA (5). The automated stepwise addition of **1** and H_2O to **3** was performed using the general procedure. The amine-terminated PEG **(3)** (20 g; 3.9 mmol; M_n = 5100 g mol^{-1}) was dissolved in NMP (120 mL) and pyridine (120 mL). The reaction time between additions was 6 h, and the reaction temperature was set to 50 °C. Before each addition of **1** a small sample was taken and precipitated into diethyl ether, filtered, and dried in vacuum at 40 °C. These samples were analyzed by GPC in DMF and chloroform. ^{1}H NMR spectra were recorded in DMSO-d_6.

MPEG-Ar$_2$-NH$_2$ (number of cycles = 1). Yield: 2.30 g; 0.44 mmol. ^{1}H NMR (300 MHz, DMSO-d_6) δ [ppm]: 5.98 (br s., 2 H, −NH_2); 6.56 (d, J = 8.8 Hz, 2 H, Ar2-C3-*H*, Ar2-C5-*H*); 6.60 (d, J = 8.6 Hz, 2 H, Ar2-C2-*H*, Ar2-C6-*H*); 7.63 (d, J = 8.5 Hz, 2 H, Ar1-C3-*H*, Ar1-C5-*H*); 7.73 (d, J = 8.5 Hz, 2 H, Ar1-C2-*H*, Ar1-C6-*H*); 10.08 (s, 1 H). GPC (DMF + 1 g/L LiBr): M_n = 6190 g/mol, M_w = 6560 g/mol, PDI = 1.06 (UV detection).

MPEG-Ar$_3$-NH$_2$ (number of cycles = 2). Yield: 2.48 g; 0.46 mmol. ^{1}H NMR (300 MHz, DMSO-d_6) δ [ppm]: 5.56 (br s, 2 H, −NH_2); 6.61 (d, J = 8.6 Hz, 2 H, Ar3-C3-*H*, Ar3-C5-*H*); 7.63 (d, J = 8.6 Hz, 2 H); 7.74 (d, J = 8.5 Hz, 1 H, Ar1-C2-*H*, Ar1-C6-*H*); 7.86−8.00 (m, 8 H, ar); 9.98−10.13 (m, 1 H, N−*H*); 10.44 (s, 1 H, N−*H*). GPC (DMF + 1 g/L LiBr): M_n = 6380 g/mol, M_w = 6780 g/mol, PDI = 1.06 (UV detection).

MPEG-Ar$_4$-NH$_2$ (number of cycles = 3). Yield: 2.60 g; 0.47 mmol. ^{1}H NMR (300 MHz, DMSO-d_6) δ [ppm]: 5.58 (br s, 2 H, −NH_2); 6.70 (d, J = 4.8 Hz, 2 H, Ar4-C3-*H*, Ar4-C5-*H*); 7.73 (d, 2 H, Ar1-C2-*H*, Ar1-C6-*H*); 7.88−8.09 (m, 12 H, ar); 10.00−10.22 (m, 1 H, N−*H*); 10.38−10.57 (m, 2 H, N−*H*). GPC (DMF + 1 g/L LiBr): M_n = 6330 g/mol, M_w = 6410 g/mol, PDI = 1.06 (UV detection).

MPEG-Ar$_5$-NH$_2$ (number of cycles = 4). Yield: 2.56 g; 0.46 mmol. ^{1}H NMR (300 MHz, DMSO-d_6): δ [ppm] = 5.58 (br s, 1 H, −NH_2); 6.68 (d, J = 7.9 Hz, 2 H, Ar5-C3-*H*, Ar5−C5-*H*); 7.74 (d, J = 8.5 Hz, 1 H, Ar1-C2-*H*, Ar1-C6-*H*); 7.84−8.21 (m, 16 H, ar); 10.03−10.18 (m, 1 H, N−*H*); 10.31−10.56 (m, 3 H, N−*H*). GPC (DMF + 1 g/L LiBr): M_n = 6480 g/mol, M_w = 6890 g/mol, PDI = 1.06 (UV detection).

MPEG-Ar$_6$-NH$_2$ (number of cycles = 5). Yield: 2.48 g; 0.43mmol. ^{1}H NMR (300 MHz, DMSO-d_6) δ [ppm]: 5.58 (br s, 2 H, −NH_2); 6.69 (d, J = 8.27 Hz, 2 H, Ar6-C3-*H*, Ar6-C5-*H*); 7.74 (d, J = 8.5 Hz, 1 H, Ar1-C2-*H*, Ar1-C6-*H*); 7.89−8.20 (m, 20 H,

Table 1. Optimization of Reaction Conditions

expt	time/h	*T*/°C	solvent[a]	% aniline-Ar_2-NH_2 (Figure 1, $n = 1$)
1	1	r.t.	NMP	25
2	2	r.t.	NMP	61
3	5	r.t.	NMP	58
4	2	50	NMP	70
5	5	r.t.	NMP:pyridine = 50:50 (v:v)	90

[a] NMP = *N*-methyl-2-pyrrolidone.

ar); 10.06−10.20 (m, 1 H, N−*H*); 10.46 (t, J = 10.8 Hz, 4 H, N−*H*). GPC (DMF + 1 g/L LiBr): M_n = 6590 g/mol, M_w = 7010 g/mol, PDI = 1.06 (UV detection).

MPEG-Ar_7-NH_2 (number of cycles = 6). Yield: 2.41 g; 0.41 mmol. ^{1}H NMR (300 MHz, DMSO-d_6) δ [ppm]: 5.74 (br s, 2 H, −NH_2); 7.81 (d, J = 6.8 Hz, 2H, Ar7-C3-*H*, Ar7-C5-*H*); 7.74 (d, J = 8.5 Hz, 1 H, Ar1-C2-*H*, Ar1-C6-*H*); 7.85−8.09 (m, 24 H,ar); 10.15 (br s, 1 H, N−*H*); 10.38−10.59 (m, 5 H, N−*H*). GPC (DMF + 1 g/L LiBr): M_n = 6790 g/mol, M_w = 7320 g/mol, PDI = 1.08 (UV detection).

MPEG-Ar_8-NH_2; PEG-OPBA (number of cycles = 7). Yield: 2.67 g; 0.45 mmol. ^{1}H NMR (300 MHz, DMSO-d_6) δ [ppm]: 5.97 (br s, 2 H, −NH_2); 7.90 (d, J = 7.35 Hz, 2 H, Ar8-C3-*H*, Ar8-C5-*H*); 7.74 (d, J = 8.5 Hz, 1 H, Ar1-C2-*H*, Ar1-C6-*H*); 7.93−8.05 (m, 28 H, ar); 10.33 (br s, 1 H, N−*H*); 10.42−10.58 (m, 6 H, N−*H*). GPC (DMF + 1 g/L LiBr): M_n = 6970 g/mol, M_w = 7480 g/mol, PDI = 1.07 (UV detection).

Synthesis of 150 g of PEG-OPBA (6). The synthesis was carried out using the general procedure. Amine-terminated PEG (**3**) (150 g; 29.3 mmol; M_n = 5100 g mol^{-1}) was dissolved in NMP (700 mL) and pyridine (700 mL) and heated to 50 °C. Monomer and water were automatically added in time intervals of 6 h. The reaction mixture was then poured into diethyl ether (5 L) at −30 °C. The light yellow precipitate was filtered and dried in vacuum. Afterward, the solid was dissolved in NMP (300 mL) and precipitated into diethyl ether (3 L) at −30 °C. The white solid was recovered by filtration and dried in vacuum. Yield: 92−98%. ^{1}H NMR (300 MHz, DMSO-d_6) δ [ppm]: 5.87 (br s, 2 H, −NH_2); 7.89 (d, J = 7.4 Hz, 2 H, Ar8-C3-*H*, Ar8-C5-*H*); 7.73 (d, J = 8.5 Hz, 1 H, Ar1-C2-*H*, Ar1-C6-*H*); 7.93−8.07 (m, 28 H, ar); 10.33 (br s, 1 H, N−*H*); 10.42−10.58 (m, 6 H, N−*H*). GPC (DMF + 1 g/L LiBr): M_n = 6400 g/mol, M_w = 6750 g/mol, PDI = 1.05 (UV detection).

Synthesis PS-OPBA (7). Amine terminated PS (**4**) (1 g) were dissolved in NMP (20 mL) and pyridine (20 mL) and heated to 50 °C. The addition of monomer and water was performed using the general procedure with a time step of 6 h. The reaction mixture was poured into methanol and the precipitated was filtered and dried in vacuum. Yield: 1.2 g (0.31 mmol, 91%). ^{1}H NMR (300 MHz, DMF-d_7) δ [ppm]: 7.89 (d, J = 8.6 Hz, 2 H); 8.06−8.20 (m, 23 H); 10.15 (s, 1 H); 10.54 (br s, 6 H). GPC (chloroform): M_n = 3400 g/mol, M_w = 3600 g/mol, PDI = 1.07 (UV detection).

Synthesis of Aniline-Ar_2-NH_2 (8). Aniline was reacted with **(1)** under different conditions using the General Procedure. Because of the fact that is has not been possible of separating the resulting products via column chromatography or HPLC, an exact yield for the desired product cannot be measured. The reaction conditions for the synthesis correspond to experiments 1−5 in Table 1.

Experiment 1. Aniline (2.08 g, 22.35 mmol); reaction time: 1 h; r.t.; NMP (48 mL); yield: 6.9 g. ^{1}H NMR (300 MHz, DMSO-d_6): δ [ppm] = 6.91 (d, J = 8.3 Hz, 2 H, Ar3-C2-*H*, Ar3-C6-*H*); 7.09 (t, J = 7.4 Hz, 1 H, Ar1-C4-*H*); 7.35 (t, J = 7.8 Hz, 2 H, Ar1-C3-*H*, Ar1−C5-*H*); 7.79 (d, J = 8.6 Hz, 2 H, Ar2-C2-*H*, Ar2-C6-*H*); 7.87 (d, J = 8.6 Hz, 2 H, Ar2-C3-*H*, Ar2-C5-*H*); 7.89 − 8.07 (m, 4 H, Ar1-C2-*H*, Ar1-C6-*H*, Ar3-C3-*H*, Ar5-C6-*H*); 10.15 (s, 1 H, N−*H*); 10.24 (s, 1 H, N−*H*).

Experiment 2. Aniline (2.41 g, 25.89 mmol); reaction time: 2 h; r.t.; NMP (60 mL); yield: 8.12 g. ^{1}H NMR (300 MHz, DMSO-d_6): δ [ppm] = 6.99 (d, J = 8.3 Hz, 2 H, Ar3-C2-*H*, Ar3-C6-*H*); 7.09 (t, J = 7.0 Hz, 1 H, Ar1-C4-*H*); 7.35 (t, J = 7.4 Hz, 2 H, Ar1-C3-*H*, Ar1-C5-*H*); 7.79 (d, J = 8.5 Hz, 2 H, Ar2-C2-*H*, Ar2-C6-*H*); 7.90 (d, J = 8.8 Hz, 2 H, Ar2-C3-*H*, Ar2-C5-*H*); 7.89−8.07 (m, 4 H, Ar1-C2-H, Ar1-C6-*H*, Ar3-C3-*H*, Ar5-C6-*H*); 10.12−10.22 (m, 1 H, N−*H*); 10.27−10.36 (m, 2 H, N−*H*).

Experiment 3. Aniline (1.23 g, 13.21 mmol); reaction time: 5 h; r.t.; NMP (25 mL); yield: 4.1 g. ^{1}H NMR (300 MHz, DMSO-d_6): δ [ppm] = 6:97 (d, J = 8.3 Hz, 2 H, Ar3-C2-*H*, Ar3−C6-*H*); 7.09 (t, J = 7.4 Hz, 1 H, Ar1-C4-*H*); 7.35 (t, J = 7.8 Hz, 2 H, Ar1-C3-*H*, Ar1−C5-*H*); 7.79 (d, J = 7.72 Hz, 2 H); 7.78 (d, J = 8.5 Hz, 2 H, Ar2-C2-*H*, Ar2−C6-*H*); 7.93−8.03 (m, 4 H, Ar1-C2-*H*, Ar1−C6-*H*, Ar3-C3-*H*, Ar5-C6-*H*); 10.11 − 10.20 (m, 1 H, N−*H*); 10.22−10.36 (m, 1 H, N−*H*).

Experiment 4. Aniline (1.10 g, 11.82 mmol); reaction time: 2 h; 50 °C; NMP (25 mL); yield: 3.5 g. ^{1}H NMR (300 MHz, DMSO-d_6): δ [ppm] = 6.95 (d, J = 8.3 Hz, 2 H, Ar3-C2-*H*, Ar3-C6-*H*); 7.09 (t, J = 6.8 Hz, 1 H, Ar1-C4-*H*); 7.35 (t, J = 7.8 Hz, 2 H, Ar1-C3-*H*, Ar1-C5-*H*); 7.79 (d, J = 8.6 Hz, 2 H, Ar2-C2-*H*, Ar2-C6-*H*); 7.88 (d, J = 8.6 Hz, 2 H, Ar2-C3-*H*, Ar2-C5-*H*); 7.91−8.07 (m, 4 H, Ar1-C2-*H*, Ar1-C6-*H*, Ar3-C3-*H*, Ar5-C6-*H*); 10.15 (s, 1 H, N−*H*); 10.24 (s, 1 H, N−*H*).

Experiment 5. Aniline (0.67 g, 7.20 mmol); reaction time: 5 h; r.t.; NMP (16 mL); pyridine (16 mL); yield: 2.12 g. ^{1}H NMR (300 MHz, DMSO-d_6): δ [ppm] = 6.91 (d, J = 8.3 Hz, 2 H, Ar3-C2-*H*, Ar3-C6-*H*); 7.09 (t, J = 7.4 Hz, 1 H, Ar1-C4-*H*); 7.34 (t, J = 7.8 Hz, 2 H, Ar1-C3-*H*, Ar1-C5-*H*); 7.79 (d, J = 8.6 Hz, 2 H, Ar2-C2-*H*, Ar2-C6-*H*); 7.86 (d, J = 8.6 Hz, 2 H, Ar2-C3-*H*, Ar2-C5-*H*); 7.84−8.03 (m, 4 H, Ar1-C2-*H*, Ar1-C6-*H*, Ar3-C3-*H*, Ar5-C6-*H*); 10.15 (s, 1 H, N−*H*); 10.24 (s, 1 H, N−*H*).

Synthesis of Aniline-Ar_1-NO_2 (9). Aniline (6.01 g; 64.5 mmol) and *p*-nitrobenzoic acid (11.98 g; 64.5 mmol) were dissolved in dry THF (100 mL) and stirred for 5 days at room temperature. After removing the solvent in vacuum the product was dried in high vacuum, yielding 15.58 g (64.4 mmol, 99.8%). ^{1}H NMR (300 MHz, DMSO-d_6): δ [ppm] = 7.09 (t, J = 8.0 Hz, 1 H, Ar1-C4-*H*,*H*); 7.44 (t, J = 8.0 Hz, 2 H, Ar1-C3-*H*,Ar1-C5-*H*); 8.16 (d, J = 7.7 Hz, 2 H, Ar2-C2-*H*, Ar2-C6-*H*); 8.31 (q, J = 9.0 Hz, 4 H, Ar1-C2-*H*, Ar1-C6-*H*, Ar2-C3-*H*, Ar2-C5-*H*); 11.45 (br s, 1 H, N−*H*).

Synthesis of Aniline-Ar_1-NH_2 (10). 9 (1.02 g; 4.2 mmol) was dissolved in DMF (100 mL), and palladium on charcoal (10 wt % Pd on C; 0.1 g) was added. The suspension was stirred for 2 days under hydrogen pressure (8 bar) at room temperature. Afterward, the suspension filtered through Celite evaporated, and the resulting white solid was dried in high vacuum. Yield: 0.88 g (4.1 mmol; 97.6%). ^{1}H NMR (300 MHz, pyridine-d_5): δ [ppm] = 5.67 (br s, 2 H, −NH_2); 6.96 (d, J = 8.5 Hz, 2 H, Ar2-C2-*H*, Ar2-C6-*H*); 7.11 (t, J = 7.4 Hz, 1 H, Ar1-C4-*H*); 7.39 (t, J = 7.6 Hz, 2 H, Ar1-C3-*H*, Ar1-C5-*H*); 8.20 (d, J = 7.7 Hz, 2 H, Ar1-C2-*H*, Ar1-C6-*H*); 8.27 (d, J = 8.6 Hz, 2 H, Ar2-C3-*H*, Ar2−C5-*H*); 10.61 (br s, 1 H).

Results and Discussion

Proposed Reaction Cycle. One of the established routes to prepare poly(*p*-benzamide) employs 4-*N*-sulfinylaminobenzoyl chloride (**1**), which is readily prepared from *p*-aminobenzoic acid and thionyl chloride (Scheme 1).[16,17]

Polymerization of 4-*N*-Sulfinylaminobenzoyl Chloride. Polymerization is typically initiated by adding water to a solution of **1**, which results in the formation of SO_2 and a primary amine which immediately reacts with the acid chloride to form a polymer (Figure 1).[16] Intrigued by the somewhat unusual reactivity of the sulfinylamine group, we decided to employ **1** in a controlled stepwise condensation to produce oligo(*p*-benzamide)s. In our proposed reaction scheme, the sulfinylamine group acts as an amine protective group that can be removed quantitatively without accumulation of either the cleavage reagent (water) or cleaved-off protective group (SO_2).[18,19] Such

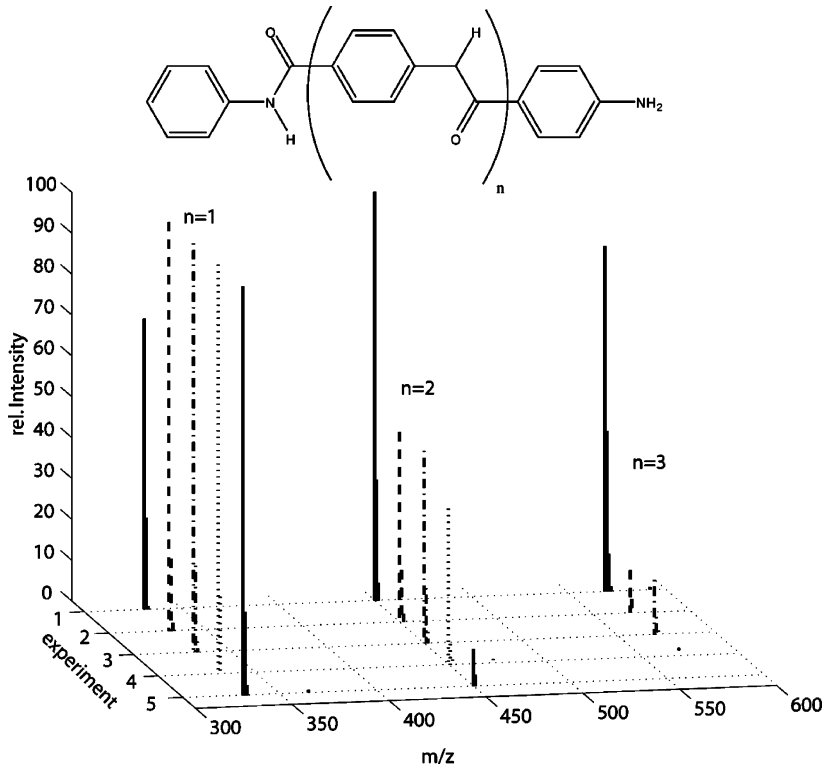
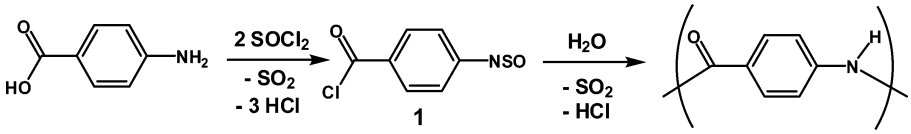
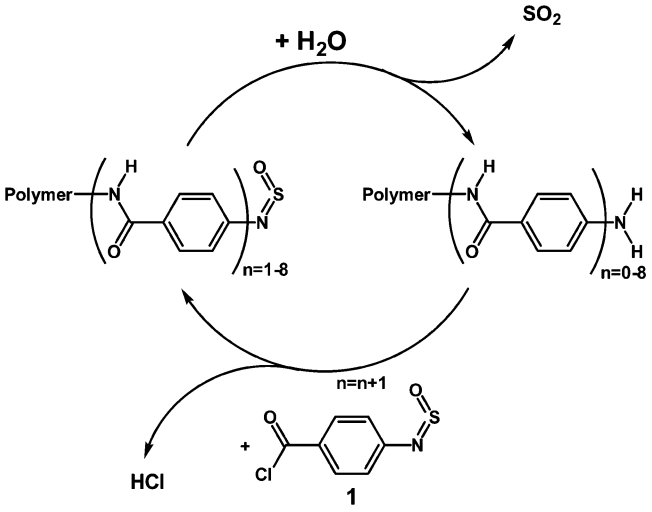


Figure 1. Field desorption mass spectra (FD-MS) taken from model reaction mixtures under different reaction conditions. The product aimed for ($n = 1$, $m/z = 331.1$ g mol^{-1}) and two side products ($n = 2$, $m/z = 450.2$ g mol^{-1}; $n = 3$, $m/z = 569.2$ g mol^{-1}) can be observed. The product distributions shown here correspond to the experiments described in Table 1.

Scheme 1. Preparation of 4-*N*-Sulfinylaminobenzoyl Chloride (1) from *p*-Aminobenzoic Acid



Scheme 2. Reaction Cycle in Which a Polymer Carrying a Terminal Primary Amine (Polymer-NH_2) Is Reacted Alternating with 1 and Water



a requirement in not easily met by most of the well-known protective groups. Compound **1** was therefore the ideal candidate for the construction of a reaction cycle in which a polymer carrying a primary amine was alternatingly reacted with **1** and water (Scheme 2).

Initially, **1** is added to the polymer that carries a terminal amine forming an amide. The sulfinylamine is now situated at the chain end of the polymer. Addition of water cleaves off SO_2 and releases the terminal primary amine which can continue to react in the next reaction cycle.

The reaction cycle is therefore situated at the boundary between classical organic synthesis and polymer synthesis. In multistep organic synthesis, protective groups would be used to ensure complete control over the oligomer growth process. Workup and purification procedures would follow each synthetic transformation, ensuring full control over the reaction. The polymer approach, on the other hand, would not require any protective groups at the expense of exact control over the molecular weight and the molecular weight distribution. In the approach proposed here, no workup procedure is carried out after the monomer addition. The protective groups (sulfinylamines) merely serve as a means of controlling the oligomerization kinetics in a "stop-and-go" fashion. The condensation of the oligomer thereby follows a pseudo-chain growth, which should allow for high levels of control over the molecular weight.

In order to evaluate the feasibility of this synthetic cycle, several studies on the nonpolymeric model compound, aniline, were carried out.

Reaction Optimization via Model Compounds. Aniline was used as a low molecular weight model compound for the amine-terminated polymer.

Two full reaction cycles as shown in Scheme 2 were carried out under different reaction conditions (up to aniline-Ar_2-NH_2). From previous experience we expected that no more than two *p*-aminobenzoic acids could be condensed onto aniline without

precipitation of the product. For these initial model studies with aniline the number of consecutive reaction cycles was therefore limited to two.

The alternating addition of precise amounts of water and monomer **1** at certain time intervals was achieved via two computer-controlled titration pumps. The hardware setup as well as the software that controlled the reaction cycle was developed in our group (see Supporting Information). The titration pumps allowed the addition of stock solutions with 0.02 mL precision.

The initial experiments were carried out at room temperature while varying the reaction time between addition of reagent **1** and H_2O from 1 to 5 h (Table 1, experiments 1−3). The reaction products were analyzed by ^{1}H NMR spectroscopy and FD-mass spectrometry.

As can be seen from Figure 1, not only the desired product, aniline-Ar_2-NH_2 (Figure 1 $n = 1$, $m/z = 331.1$ g mol^{-1}), was formed but also longer oligomers (aniline-Ar_3-NH_2, Figure 1, $n = 2$, $m/z = 450.2$ g mol^{-1}; aniline-Ar_4-NH_2, Figure 1, $n = 3$, $m/z = 569.2$ g mol^{-1}). As can be seen from Figure 1, the amounts of longer oligomeric side products decreased with increasing reaction times. ^{1}H NMR spectroscopic analysis of the raw product mixtures confirmed this trend. It is likely that at shorter reaction times water was added to the reaction mixture prematurely, i.e., before the amide formation was completed. This probably resulted in the amine deprotection of unreacted monomer **1**, its oligomerization, and reaction with aniline.

An increase in temperature while shortening the reaction time to 2 h (Table 1, experiment 4) resulted in a more favorable product distribution (Figure 1). The side product aniline-Ar_4-NH_2 (Figure 1, $n = 3$) could not be observed any longer by FD mass spectrometry or ^{1}H NMR spectroscopic analysis.

It has been reported that the presence of pyridine accelerates the hydrolysis of the sulfinylamine group.[20] We therefore carried out a further model experiment (Table 1, experiment 5) in the presence of pyridine at room temperature with reaction times of 5 h. Figure 1 shows the dramatic effect pyridine has on the distribution of oligomeric side products. The only side product that could be observed (aniline-Ar_3-NH_2, Figure 1 $n = 2$) is present at less than 10% (according to FD-MS). These promising results encouraged us to examine whether the reaction could be carried out with a amine-terminated polymer instead of the low molecular weight aniline.

Large-Scale Rod−Coil Copolymer Synthesis. In order to compare the rod−coil copolymers produced by the automated synthesis with the ones prepared and analyzed in detail previously,[8−10,12,13] we chose PEG as the coil block for our initial investigations. PEG monomethyl ether ($M_n = 5000$ g mol^{-1}) was reacted with *p*-nitrobenzoyl chloride to form the corresponding ester. The nitro group was subsequently reduced to a primary amine, as reported previously.[8]

We anticipated that a reaction at the chain end of a polymer would require harsher conditions than the aniline model examined in the preceding section. We therefore used the most promising reaction conditions (Table 1, experiment 5) but additionally increased the temperature to 50 °C.

The amine-terminated PEG (20 g) was dissolved in NMP/pyridine mixture (v:v = 50:50) at 50 °C. Monomer **1** and water were added in an alternating fashion in 5 h intervals while stirring the reaction mixture mechanically at 50 °C. Samples were taken after each reaction cycle (just prior to adding monomer **1**). After seven reaction cycles the reaction was stopped, and the polymer was recovered by precipitation into diethyl ether to give a PEG−OPBA rod−coil copolymer (Figure 2, top).

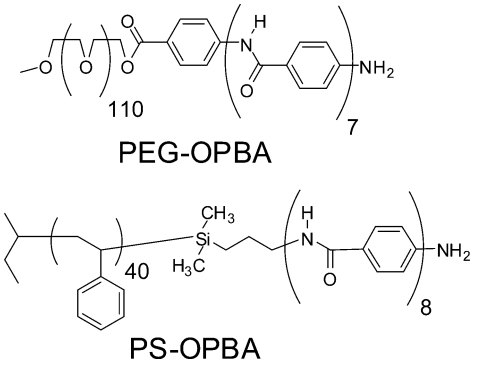


Figure 2. Oligo(*p*-benzamide) (OPBA) copolymers with poly(ethylene glycol) (PEG) and poly(styrene) (PS) coil block as prepared via the automated reaction cycle shown in Scheme 2.

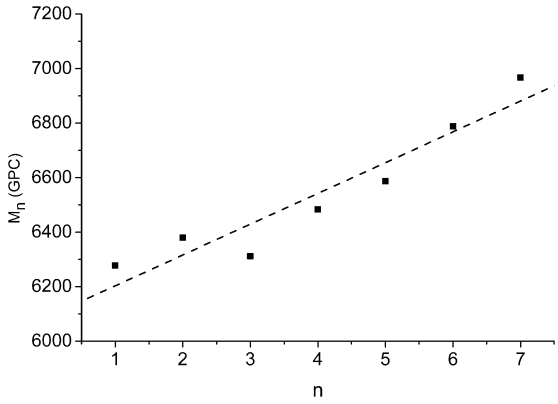


Figure 3. Plot of the apparent number-average molecular weight (M_n) of poly(ethylene glycol)-*block*-oligo(*p*-benzamide) (PEG-OPBA) determined by gel permeation chromatography (GPC) in *N*,*N*-dimethylformamide (DMF) against the number of reaction cycles *n* (linear fit shown as a dashed line).

The samples taken after each reaction cycle were analyzed by GPC in DMF and chloroform (see Supporting Information) and ^{1}H NMR spectroscopy. The GPC data in DMF showed the molecularly dissolved copolymer as well as traces of oligomers that were not attached to PEG.

Interestingly, plotting the apparent molecular weights of the PEG copolymer samples, determined by GPC in DMF, against the number of reaction cycles gave a remarkably linear relationship (Figure 3).

The number-average molecular weight shifts systematically toward higher molecular weights with increasing number of reaction cycles. This clearly shows that a very high level of control over the molecular weight of the growing OPBA is achieved with this automated stepwise synthesis.

The chloroform GPC traces showed the typical aggregation peaks similar to those observed before.[9] ^{1}H NMR spectroscopic data were also in good agreement with reported data.[8] These promising results inspired us to repeat the synthesis on a much larger scale. The reaction was carried out once more on 150 g of amine functionalized PEG. All analyses of the copolymer product were identical to the product prepared on the 20 g scale.

In order to further demonstrate the versatility of this new automated synthetic approach, we prepared an amine functionalized polystyrene ($M_n = 2950$ g mol^{-1}) via anionic polymerization. The living carbanion was quenched with dimethylchlorosilane and subsequently hydrosilylated onto allylamine. The presence of an amine functionality directly attached to the PS allowed us to introduce the polymer into the reaction cycle without further functionalization. After eight reaction cycles under identical conditions to those of the PEG copolymer

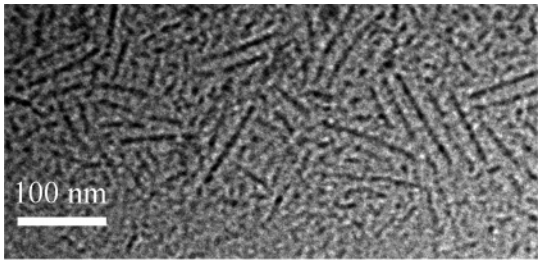


Figure 4. Transmission electron microscopy (TEM) image (unstained) of poly(ethylene glycol)-*block*-oligo(*p*-benzamide) copolymer (PEG−OPBA, Figure 3 $n = 7$) drop-cast from chloroform solution onto carbon-coated copper grids.

prepared before, the polymer (1.2 g) was precipitated into methanol to give a PS−OPBA block copolymer (Figure 2, bottom). ^{1}H NMR spectroscopic analysis of the copolymer was inconclusive as the aromatic signals of the OPBA block were hidden under the broad PS phenyl signals. GPC analysis of the PS−OPBA copolymer in chloroform only showed a high molecular weight aggregate of low intensity (see Supporting Information). Most of the polymer eluted as the molecularly dissolved unimer ($M_n = 3400$ g mol^{-1}).

When chloroform was added to solid PS−OPBA, a turbid solution was obtained. Filtration of this PS−OPBA solution through a 0.45 μm syringe filter resulted in a particularly high back-pressure which is an indication for very high molecular weight polymers or aggregates. The clear filtrate, which was presumably freed of the aggregates, was used for the GPC analysis described above.

To unambiguously show the existence of high molecular weight aggregates, transmission electron microscopy (TEM) images were recorded from chloroform solutions of PEG−OPBA and PS−OPBA drop-cast onto carbon-coated copper grids.

The TEM images of PEG−OPBA show extremely rigid-rod-like micelles with a uniform width of ca. 9 nm (Figure 4). The images obtained are strikingly similar to those observed for the precisely defined polymers prepared via laborious solution syntheses.[12,13]

The PS−OPBA copolymer solution was also investigated by TEM before and after filtration (0.45 μm syringe filter). Bundles of fiberlike aggregates could be seen (Figure 5, top) for the solution that was not passed though a syringe filter. The size of these bundles of fibers exceeds the pore size of the syringe filter used for filtration. As expected, the images of the filtered solution did not show large aggregated bundles but revealed individual fiberlike structures (Figure 5, bottom). Association of the aggregates into bundles of high molecular weight is therefore most likely the reason for the high back-pressure observed during the syringe filtration of the sample. The individual PS−OPBA aggregates (Figure 5, bottom) do not appear to form micelles that are as rigid as the ones observed for PEG−OPBA. However, micellar aggregates can be seen with a perfectly uniform width of ca. 10 nm.

The reason why the PS−OPBA copolymer forms bundles of fibers whereas the PEG−OPBA shows well-defined and separated linear aggregates is unknown at present. Syntheses of precisely defined PS−OPBA copolymers with different coil block volume fractions are currently being carried out and will be reported separately.

It is necessary to emphasize at this point that the block copolymers forming such outstandingly well-defined aggregation structures were synthesized in large quantities via an automated reaction cycle. The data presented here clearly show that the

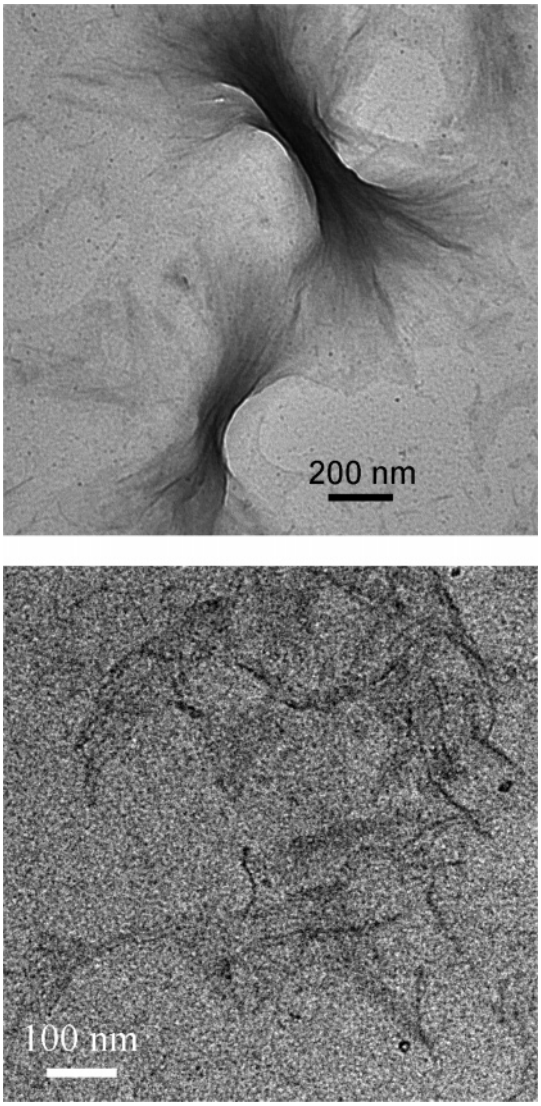


Figure 5. Transmission electron microscopy (TEM) images (unstained) of poly(styrene)-*block*-oligo(*p*-benzamide) (PS−OPBA, $n = 8$) drop-cast from chloroform solution onto carbon-coated copper grids. Top: without syringe filtration. Bottom: after syringe filtration.

stepwise addition of 4-*N*-sulfinylaminobenzoyl chloride and water to amine-terminated polymers results in well-defined rod−coil block copolymers. However, any multistep reaction that is carried out without workup after each reaction step will eventually accumulate side products, give faulty sequences and result in a molecular weight distribution. In the work presented here, only small amounts of oligomers are observed that are not attached to the polymer after eight reaction cycles. Even though the amount of residual oligomers is small, it has to be assumed that the polymer bound oligomers also show a certain molecular weight distribution. In this case it is even more astonishing that the copolymers form such extremely well-defined aggregates as observed by TEM. It appears that small deviations in the oligomer length of the rod−coil copolymer can be averaged out such that the aggregate presents itself similarly to those of the precisely defined monodisperse copolymers.

It would be important to establish the effect of polydispersity in the OPBA block on the aggregation phenomena observed by TEM. Such investigations are currently being carried out in our laboratories using mixtures of precisely defined rod−coil copolymers.

In conclusion, we have developed an automated repetitive synthesis for the stepwise growth of oligo(*p*-benzamide)s onto amine-terminated polymer chains. The synthesis allows the preparation of rod−coil copolymers on the 100 g scale and has potential to be scaled up further. Very good control over the oligomer length can be achieved as was evidenced by a linear relationship between the molecular weight of the copolymer and the number of reaction cycles carried out. Poly(ethylene glycol) and polystyrene monoamines were prepared and investigated in the automated synthesis cycle. TEM analysis of the copolymers showed linear rigid-rod-like aggregates of uniform width. This new synthetic approach makes supramolecular oligo(*p*-benzamide) block copolymers accessible in unprecedented quantities. If supramolecular polymers are to play a role in applications such as coatings, additives for blends, surfactants, adhesives etc., synthetic routes need to be in place that ensure the availability of sufficient quantities of materials required for bulk testing. We believe that the approach described here is a very important first step which is necessary for developing new applications in the field of supramolecular polymer chemistry.

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Supporting Information Available: Additional TEMs, GPCs, and reaction schemes. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Lee, M.; Cho, B. K.; Zin, W. C. *Chem. Rev.* **2001**, *101*, 3869−3892.
(2) Klok, H. A.; Lecommandoux, S. *Adv. Mater.* **2001**, *13*, 1217−1229.
(3) Burkoth, T. S.; Benzinger, T. L. S.; Jones, D. N. M.; Hallenga, K.; Meredith, S. C.; Lynn, D. G. *J. Am. Chem. Soc.* **1998**, *120*, 7655−7656.
(4) Rosler, A.; Klok, H. A.; Hamley, I. W.; Castelletto, V.; Mykhaylyk, O. O. *Biomacromolecules* **2003**, *4*, 859−863.
(5) Hamley, I. W.; Ansari, A.; Castelletto, V.; Nuhn, H.; Rosler, A.; Klok, H. A. *Biomacromolecules* **2005**, *6*, 1310−1315.
(6) Hentschel, J.; Borner, H. G. *J. Am. Chem. Soc.* **2006**, *128*, 14142−14149.
(7) Jahnke, E.; Lieberwirth, I.; Severin, N.; Rabe, J. P.; Frauenrath, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 5383−5386.
(8) Abbel, R.; Frey, H.; Schollmeyer, D.; Kilbinger, A. F. M. *Chem.−Eur. J.* **2005**, *11*, 2170−2176.
(9) Abbel, R.; Schleuss, T. W.; Frey, H.; Kilbinger, A. F. M. *Macromol. Chem. Phys.* **2005**, *206*, 2067−2074.
(10) Schleuss, T. W.; Abbel, R.; Gross, M.; Schollmeyer, D.; Frey, H.; Maskos, M.; Berger, R.; Kilbinger, A. F. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 2969−2975.
(11) Konig, H. M.; Abbel, R.; Schollmeyer, D.; Kilbinger, A. F. M. *Org. Lett.* **2006**, *8*, 1819−1822.
(12) Seyler, H.; Berger-Nicolette, E.; Kilbinger, A. F. M. *J. Mater. Chem.* **2007**, DOI: 10.1039/b617598h.
(13) Konig, H. M.; Gorelik, T.; Kolb, U.; Kilbinger, A. F. M. *J. Am. Chem. Soc.* **2007**, *129*, 704−708.
(14) Hawker, C. J.; Wooley, K. L. *Science* **2005**, *309*, 1200−1205.
(15) Gilman, H.; Haubein, A. H. *J. Am. Chem. Soc.* **1944**, *66*, 1515−1516.
(16) Kwolek, S. L.; Morgan, P. W.; Schaefgen, J. R.; Gulrich, L. W. *Macromolecules* **1977**, *10*, 1390−1396.
(17) Taylor, E. C.; Fletcher, S. R.; Sabb, A. L. *Synth. Commun.* **1984**, *14*, (10), 921−924.
(18) Dawson, T. L. Ph.D. Thesis, University of Kentucky, 1960.
(19) Ivanova, E. V.; Muchall, H. M. *Can. J. Chem.* **2005**, *83*, 1588−1596.
(20) Mironova, D. F.; Konoplya, O. Y. *Ukr. Khim. Zh. (Russ. Ed.)* **1976**, *42*, 374−378.

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