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High Stability of the Polyproline II Helix in Polypeptide Bottlebrushes

Afang Zhang* and Yifei Guo[a]

Abstract: Polymer bottlebrushes with monodisperse oligoproline side chains were efficiently synthesized, and the conformation of the peptide side chains in different solvents was investigated. Polymers with number-average degrees of polymerization (DP_n) of 89 and 366 were obtained by polymerization of the macromonomer in *i*PrOH/MeCN (1:1) and hexafluoroisopropanol, respectively. Circular dichroism (CD) spectra of the bottlebrush polymers in the neutral and charged states reveal that the oligoproline side chains attain stable polyproline II (PPII) helical conformations not only in aqueous solution, but also in aliphatic alcohol solutions. Dense attachment of oligopeptides onto a linear polymer chain did not lead to an increase in helix content. The possible effects of the main-chain length on the conformational stability were examined. The switching between the polyproline I (PPI) and PPII helical conformations for the oligoproline side chains in aliphatic alcohol solutions is believed to be inhibited by the overcrowded structure in the polymer bottlebrushes.

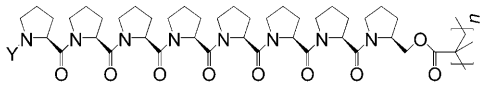
Keywords: conformation analysis · helical structures · peptides · polymerization · proline

Introduction

Synthetic macromolecules with tunable helical structures are increasingly interesting for the design of molecular devices and chiral materials.[1] Helical structures can be formed through either covalent bonds[2] or noncovalent interactions[3] and can be divided into dynamic[4] and static[5] types. Recently, the conformational stability of helices in peptides has drawn considerable attention due to its crucial influence on the functions and bioactivities of these biomacromolecules.[6]

An intriguing class of helical polymers are oligoprolines, which are well known to adopt predominately two different helical conformations: polyproline I (PPI) and polyproline II (PPII).[7] The former, which is favored in aliphatic alcohols, is a compact, right-handed helix with 3.3 repeat units per turn (5.6 Å) and all amide bonds in the *cis* conformation. The latter, favored in aqueous solution, fluorinated solvents, or organic acids, is a stretched, left-handed helix with 3 repeat units per turn (9.4 Å) and all amide bonds in the *trans* conformation. PPII is found to be a common secondary structure in natural proteins, which plays important roles in many biological processes,[8] such as protein–protein recognition and cell penetration.[9] These two distinguished conformations are interchangable by *cis–trans* isomerization of the peptide bonds.[10] They can be differentiated by optical rotation,[10b,11] NMR spectroscopy,[12] and circular dichroism (CD) spectropolarimetry.[13] The stability of these helical conformations is not only based on the solvent polarity but is also related to the concrete chemical structure of the proline repeat units. 4-Substituted prolines, such as 4-fluoroproline[14] or 4-azidoproline,[15] have a strong propensity to form the more stable PPII. In addition, the longer the oligoprolines, the greater the stability of the PPI helix in *n*-propanol.[16] Depending on the nature of the N and C termini, the threshold for oligoprolines to adopt the PPI conformation is between three and five residues.[13a,17] Conformational transitions between PPI and PPII have also been observed in oligoproline-based dendrimers.[18]

Given the considerable steric congestion encountered by pendent substituents in bottlebrush polymers,[19] we won-



poly(**1**): Y = Boc

de-poly(**1**): Y = H ·TFA

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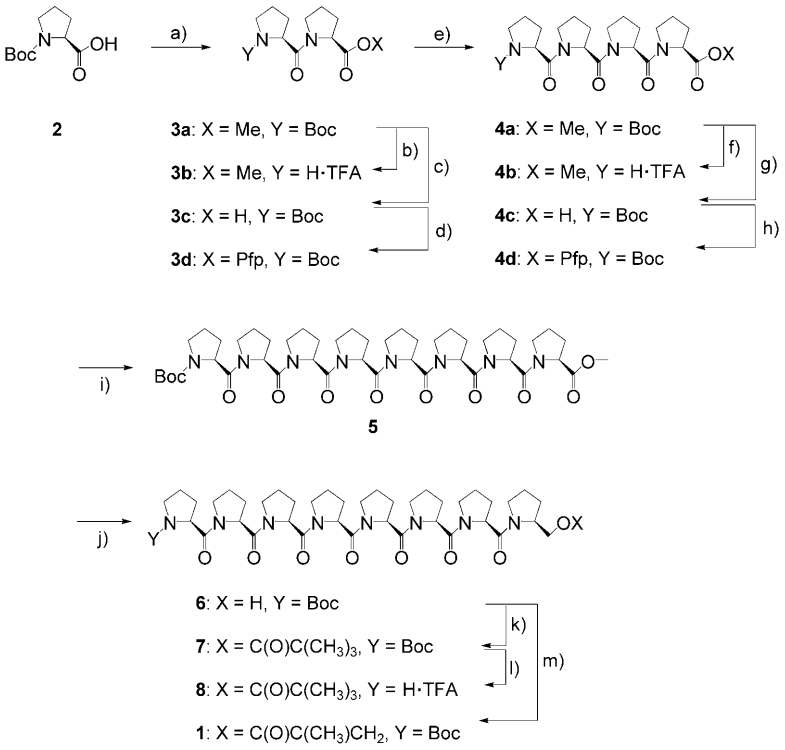
dered whether placing linear oligoproline units in close proximity by attaching them to each repeat unit of a linear polymer could be a way to force them into the less tight PPII conformation. Herein, we report on the synthesis and conformational peculiarities of a novel type of polypeptide bottlebrush[20] with monodisperse L-proline octamers as side chains and polymethacrylate as the backbone. We investigate how the conformational stability of the helices, as well as the transition between PPI and PPII, is influenced by the macromolecular architecture. To our knowledge, this is the first example of an investigation into the effects of architecture, rather than chemical modification, on the stability of oligoproline helices.



Scheme 1. Synthesis procedures for macromonomer **1**: a) EDC, HOBt, Pro-OMe·HCl, TEA, CH_2Cl_2/DMF, −30 to 25 °C, 14 h, 80 %; b) TFA, CH_2Cl_2, MeOH, −0 to 25 °C, 6 h, 100 %; c) LiOH·H_2O, MeOH/H_2O, −5 to 25 °C, 14 h, 90 %; d) Pfp-OH, EDC, CH_2Cl_2, 25 °C, overnight, 92 %; e) **3b**, **3d**, TEA, DMF, 25 °C, overnight, 70 %; f) TFA, CH_2Cl_2, MeOH, −0 to 25 °C, 6 h, 100 %; g) LiOH·H_2O, MeOH/H_2O, −5 to 25 °C, 14 h, 70 %; h) Pfp-OH, EDC, CH_2Cl_2, 25 °C, overnight, 86 %; i) **4b**, **4d**, DiPEA, DMF, 25 °C, overnight, 74 %; j) $NaBH_4$, LiCl, THF, −5 to 25 °C, 24 h, 80 %; k) trimethylacetyl chloride, THF, TEA, −0 to 25 °C, 4 h, 86 %; l) TFA, CH_2Cl_2, MeOH, 25 °C, 5 h, 100 %; m) MAC, TEA, DMAP, THF, −0 to 25 °C, 4 h (80 %). Boc: *tert*-butoxycarbonyl; DiPEA: diisopropylethylamine; DMAP: 4-dimethylaminopyridine; EDC: *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride; HOBt: *N*-hydroxybenzotriazole; MAC: methacryloyl chloride; Pfp: pentafluorophenyl; TEA: triethylamine; TFA: trifluoroacetic acid.

Results and Discussion

Synthesis: Oligoprolines and the corresponding macromonomer **1** were synthesized on multigram scales by solution peptide synthesis, in analogy to previous procedures (Scheme 1).[21] Coupling of the commercially available compound Boc-L-proline (**2**) with L-proline methyl ester in the presence of EDC and HOBt afforded Boc-protected dimer **3a**. Deprotection with TFA yielded the salt **3b**. Saponification with LiOH formed the dimer acid **3c**, which was then treated with pentafluorophenol and converted into the active ester **3d**. The tetramer ester **4a** was prepared by directly coupling **3b** with **3d**. By similar procedures to those mentioned above, this ester was converted into the salt **4b** and the active ester **4d**. Finally, the octamer ester **5** was obtained from **4b** and **4d** in yields of 72–78 % on a multigram scale. Reduction of **5** with $NaBH_4$ and LiCl afforded alcohol **6** with a yield of 80 %. The reaction of **6** with methacryloyl chloride afforded macromonomer **1** in a yield of 80 %. For conformation comparisons, model compounds **7** and **8** were also prepared. All compounds were characterized as analytically pure materials by ^1H and ^{13}C NMR spectroscopy, as well as by high-resolution mass spectrometry.

Polymerization: Conventional radical polymerization of **1** initiated with AIBN was conducted in either *i*PrOH/MeCN (1:1) or hexafluoroisopropanol (HFIP) at 60 °C and provided the polypeptide bottlebrush poly(**1**). These two solvents were initially chosen because it was expected that the oligoproline unit would attain different conformations in these

Abstract in Chinese:

本文报道了一种新型多肽分子刷的有效合成、并对其在溶液中的二次构象进行了研究。这种多肽分子刷是由单分散的脯氨酸八肽为侧链、聚甲基丙烯酸酯为主链而组成，通过大单体路线制备而成。相应大单体在不同溶剂中的自由基聚合反应提供了主链长度不同的多肽分子刷。采用圆二色谱法对这类分子刷在溶液中的二次构象分析发现：与自由脯氨酸八肽在水及正丙醇中分别呈现 PPII 及 PPI 螺旋构象、且这两种构象随溶剂的变化可以相互转化所不同的是，分子刷的脯氨酸八肽侧链在水及正丙醇中均呈现 PPII 型构象。这种螺旋构象不仅具有很高的热稳定性而且与聚合物主链链长关系甚微。经三氟乙酸脱除表面 Boc 保护基后，分子刷中的脯氨酸八肽侧链在水及正丙醇中仍呈现稳定的 PPII 型构象。我们认为脯氨酸八肽侧链在不同溶剂中的螺旋构象转化受阻是由于分子刷中侧链的高堆积密度形成的位阻所致。这种高位阻迫使相应的多肽侧链只能呈现比较伸展的 PPII 型螺旋构象。

solvents, which could impact on the polymerization behavior in different ways.[22] In macromonomer polymerization, a high concentration of the reactive species is a prerequisite for achieving high-molar-mass polymers[23] and we, therefore, decided to use 0.53 M solutions. Typical polymerization results are compiled in Table 1. The molar masses of the polypeptide bottlebrushes were determined by GPC with DMF as the eluent and universal calibration. Poly(**1**) was obtained from *i*PrOH/MeCN and HFIP with main-chain number-average degrees of polymerization (DP_n) of approximately 89 and 366, respectively. The considerable difference in the DP_n values for the resultant bottlebrush polymers may be explained by assuming the presence of different conformations for the same macromonomer in the different polymerization media. Both bottlebrush polymers showed excellent solubility in different solvents, such as water, MeOH, CH_2Cl_2, *i*PrOH, and *n*PrOH. To check the possible effects of charges on the conformational stability of the oligopeptide side chains, the Boc groups in poly(**1**) were removed with TFA to furnish the positively charged bottlebrush polymer de-poly(**1**). ^{1}H NMR spectra of poly(**1**) and de-poly(**1**) were recorded at 80 °C in [D_6]-dimethylsulfoxide ([D_6]DMSO) to achieve better resolution and, thus, a basis for the assessment of the backbone tacticity. Based on these spectra, the polymers contain around 63 % syndiotactic triads, irrespective which solvent was used for the polymerization (see Figure S2 in the Supporting Information).[24] This tacticity is close to that of poly(methyl methacrylate) synthesized by conventional free-radical polymerization in DMF at 60 °C (containing ≈62 % syndiotactic triads).[25] Therefore, the chiral substituent of the macromonomer and the polymerization solvents did not show any obvious influence on the stereochemical course of monomer addition.

Table 1. Conditions for and results of the radical polymerization of **1**.

Entry	Polymerization conditions[a]		Yield [%]	GPC[b]		
	[**1**] [mmol L^{-1}]	[AIBN] [mmol L^{-1}]		M_n ($\times 10^{-4}$)	PDI	DP_n[e]
1[c]	527	15.2	87	8.4	2.14	89
2[d]	527	15.2	82	34.7	2.53	366

[a] In DMF at 60 °C with AIBN as the initiator, 12 h. [b] DMF as the eluent at 40 °C. [c] Isopropanol/acetonitrile 1:1 as the polymerization solvent mixture. [d] HFIP as the polymerization solvent. [e] DP_n represents the number-average degree of polymerization of the main chain.

Conformation: The conformation of the oligoproline side chains in poly(**1**) at different temperatures and in different solvents was investigated with circular dichroism (CD) spectroscopy (Figure 1). Typical CD spectra for PPII helices (a weak positive band at 228 nm and a strong negative band at

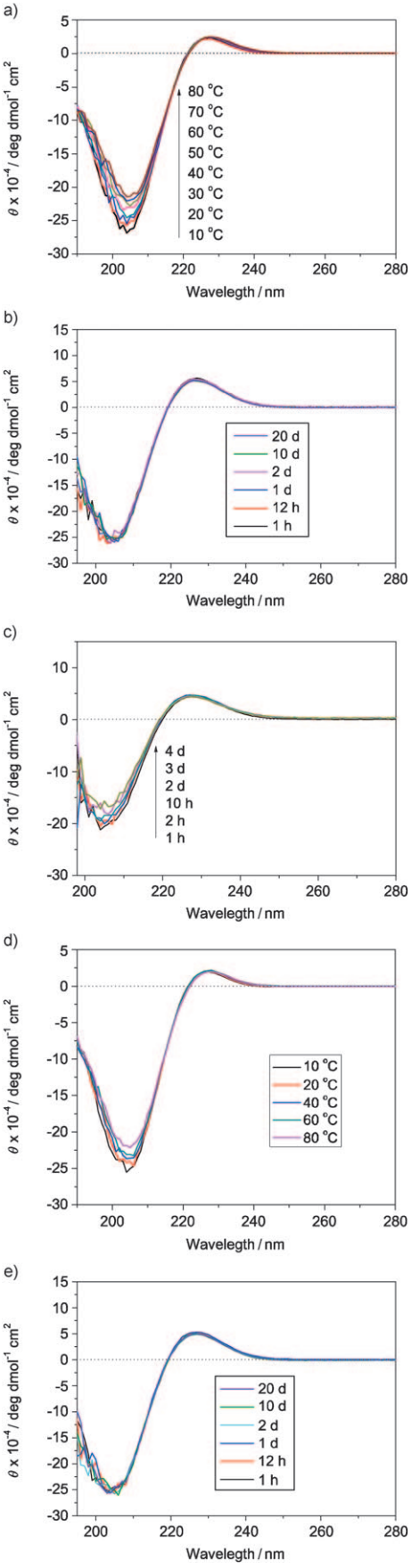


Figure 1. CD spectra of poly(**1**) (DP_n=366) in aqueous solution in the temperature range 10–80 °C (a), in *n*PrOH at 25 °C (b), and in *n*PrOH at 70 °C (c), as well as the CD spectra of poly(**1**) (DP_n=89) in water in the temperature range 10–80 °C (d) and in *n*PrOH at 25 °C (e).

204 nm)[13] were obtained from an aqueous solution of the long poly(**1**) ($DP_n = 366$). This conformation was retained at up to 80 °C without significant change (Figure 1a). In contrast to free linear oligoprolines, the proline octamers in poly(**1**) also adopted the PPII conformation in *n*PrOH at 25 °C, and the spectral characteristics stayed unchanged for 20 days (Figure 1b). In addition, this conformation was even retained at 70 °C for four days without obvious spectral changes (Figure 1c). The temperature-dependent CD spectra of the short poly(**1**) ($DP_n = 89$) in aqueous solution were also recorded, and the PPII conformation was found to be retained up to 80 °C (Figure 1d). The short poly(**1**) also yielded CD spectra with the characteristics of 100% PPII in *n*PrOH; like those of the long poly(**1**), these spectra remained unchanged for 20 days (Figure 1e). All of the above results suggest that the main-chain length does not have a significant influence on the surprising stability of the PPII conformation, at least within the range of main-chain lengths investigated.[26]

The conformation of the oligoproline side chains in deprotected polymer bottlebrush de-poly(**1**) was also examined with CD spectroscopy. As expected, the oligoproline side chains in the long de-poly(**1**) ($DP_n = 366$) adopted the PPII conformation in aqueous solution; this conformation was stable within a temperature range of 25–75 °C (Figure 2a). This behavior very much resembles that for the proline octamer **8** (inset in Figure 2a). In a comparison of the intensities of the CD signals for de-poly(**1**) with those for **8**, no increase in helix content is observed for oligopeptides attached densely onto a linear polymer chain, which suggests that there is no cooperative interaction between the neighboring oligoproline chains. The conformation of the oligoproline side chains in the de-poly(**1**) in aliphatic alcohols, such as *n*PrOH and MeOH, was also examined. CD spectra with the characteristics of 100% PPII helix were retained after the *n*PrOH or MeOH solution was kept at room temperature for 20 or 40 days, respectively (Figure 2b); this proves that the oligoproline side chains in the long de-poly(**1**) also adopted the stable PPII conformation in these solvents. For comparison, CD spectra for the model compound **8** in *n*PrOH were recorded under the same conditions (inset in Figure 2b). This oligoproline started to adopt the PPI conformation in less than 1 h, and showed the characteristics of 100% PPI helix (a weak negative band at 232 nm, a medium positive band at 214 nm, and a medium negative band at 202 nm) after 24 h. CD spectra of the short de-poly(**1**) ($DP_n = 89$) in water (Figure 2c) and *n*PrOH (Figure 2d) were recorded to check the effect of the main-chain length on the PPII-conformation stability. These spectra very much resemble the corresponding spectra for the long de-poly(**1**) ($DP_n = 366$), a result that suggests negligible effects of the main-chain length. Therefore, attachment of the oligoprolines densely on a linear polymer chain forces the peptide side chains to adopt only the PPII helical conformation in different solvents and over a broad temperature range.

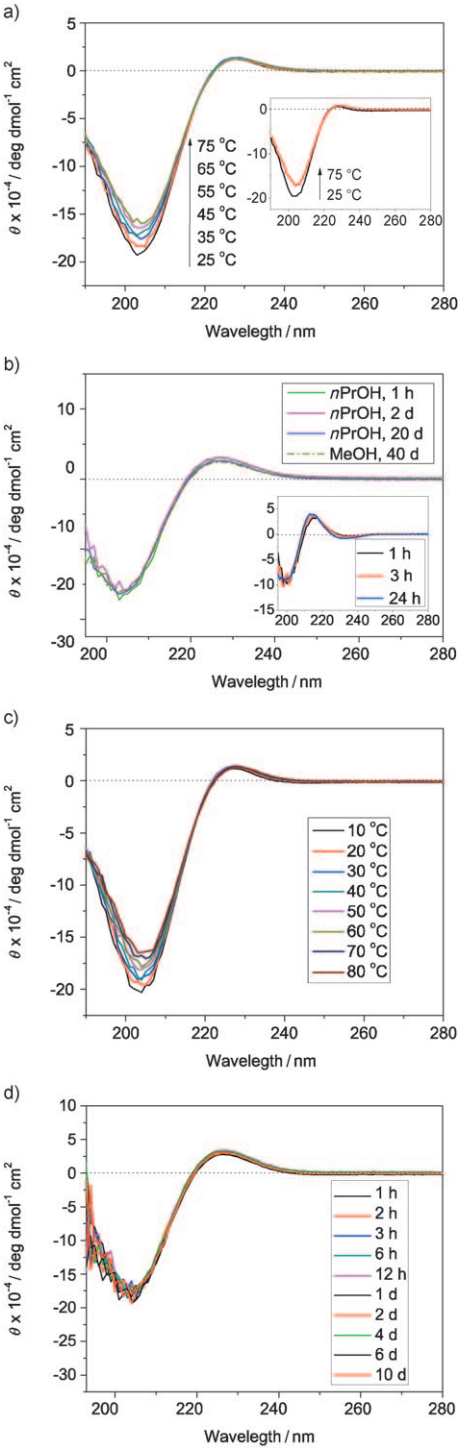


Figure 2. CD spectra of de-poly(**1**) ($DP_n = 366$) in aqueous solution in the temperature range 25–75 °C (a; inset: spectra of **8** in water) and in aliphatic alcohol solvents at 25 °C (b; inset: spectra of **8** in *n*PrOH), as well as the CD spectra of de-poly(**1**) ($DP_n = 89$) in water in the temperature range 10–80 °C (c) and in *n*PrOH at 25 °C (d).

Conclusion and Outlook

We have presented the efficient synthesis of polypeptide bottlebrushes with monodisperse oligoprolines as the side

chains and polymethacrylate as the main chain through radical polymerization of the corresponding macromonomer. CD investigations revealed that the oligoproline side chains in the cylindrical bottlebrush polymers attained a stable PPII helical conformation not only in aqueous solution but also in aliphatic alcohol solutions over a broad temperature range. The helical-conformation switching between PPII and PPI in aliphatic alcohol solutions is not observed. We attribute this to the dense packing of the proline oligomers along the polymer backbone, which forces them to adopt only the stretched PPII conformation. The main-chain length and removal of Boc groups from the periphery show negligible effects on the PPII-conformation stability. This enforced stretching could, in future, possibly be used in the opposite way, namely to stretch the main chain of a related bottlebrush polymer into a more extended conformation by finding out how to fold the peptidic substituents from PPII into PPI conformations. Further investigation could also include raising the threshold of side-chain length for stability of helical conformations. The successful construction of macromolecules with unprecedentedly stable helical conformations of their peptidic side chains could help to shine a new light on the relationship between the structure and bioactivity of biomacromolecules, such as collagen. Such stable helices could also be useful as chiral scaffolds for supramolecular helical-structure formation.

Experimental Section

Materials: AIBN was recrystallized twice from methanol. TEA and DiPEA were dried over NaOH pellets. THF and dioxane were dried by refluxing over sodium. CH_2Cl_2 was dried over CaH_2. MAC was freshly distilled before use. Other reagents and solvents were purchased from Acros or Aldrich and used as received unless otherwise stated.

Instrumentation: ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300 MHz (^{1}H: 300; ^{13}C: 75 MHz) spectrometer in either $CDCl_3$ or [D_6]DMSO solution at room temperature. High-resolution ESI mass measurements were carried out on a Waters a-Tof Micro spectrometer with an electrospray-ionization source. GPC measurements were carried out at 40 °C by using a PL-GPC 50 instrument equipped with two PL-gel 5 μm Mixed-C columns (300×7.5 mm), a differential refractive index, and viscosity (Viscotek) detectors. The system was operated with DMF (containing 1 g L^{-1} LiBr) as the eluent at a flow rate of 1 mL min^{-1}. Universal calibration was performed with poly(methyl methacrylate) standards in the molar-mass range of $M_p = 2.93\times10^3$–7.50×10^6 Da (Polymer Laboratories Ltd, UK). Column chromatography was performed by using 300–400 mesh silica gel. CD measurements were performed on a JASCO J-715 spectropolarimeter (continuous scanning mode; scanning speed: 20 nm min^{-1}; data pitch: 1 nm; response: 1 s; band width: 5.0 nm). A thermocontrolled quartz cell with a pathlength of 1 mm was used with peptide solutions containing approximately 3–5×10^{-6} dmol mL^{-1} per octamer residue. CD data are given as mean molar ellipticities based on octamer residuals (θ in deg dmol^{-1} cm^2). All samples were equilibrated for at least 12 h before measurement, except for the time-dependent measurements in *n*PrOH. The spectra are the result of five accumulations for the measurements in aqueous and *n*PrOH solutions or of one scan for the time-dependent measurements in *n*PrOH. The blank spectrum of the solution was always subtracted.

Compound 3a: HOBt in *N*-methylpyrrolidine (31 mL, 31.00 mmol) was added to a solution of Boc-Pro-OH (6.6 g, 30.60 mmol) in dry CH_2Cl_2 (80 mL) at room temperature. After 10 min, EDC (6.30 g, 30.60 mmol) was added at −30 °C, and the reaction mixture was stirred until the EDC was completely dissolved. A solution of TEA (6.06 g, 60.00 mmol) and Pro-OMe·HCl (6.00 g, 36.35 mmol) in DMF/CH_2Cl_2 (1:1, 120 mL) was then added dropwise at −30 °C. The resulting mixture was warmed to room temperature and stirred for 14 h. After successive washing of the mixture with aqueous $NaHCO_3$ and brine, the separated organic phase was dried over $MgSO_4$. After evaporation of the solvent in vacuo, the product was purified by column chromatography (ethyl acetate/hexane 1:2 to 1:1) to afford a colorless solid product (7.98 g, 80 %). ^{1}H NMR ($CDCl_3$): δ = 1.36, 1.42 (ds, 9H; Boc), 1.79–2.13 (m, 8H; CH_2), 3.35–3.75 (m, 7H; CH_2, CH_3), 4.35–4.57 ppm (m, 2H; CH); ^{13}C NMR ($CDCl_3$): δ = 23.54, 24.05, 24.98, 25.03, 28.36, 28.50, 28.71, 28.81, 29.05, 29.99, 46.47, 46.66, 46.85, 52.05, 52.15, 57.69, 57.75, 58.68, 79.43, 154.48, 171.15, 172.91 ppm; HRMS: *m*/*z*: calcd: 327.18 [*M*+H]$^+$; found: 349.1730 [*M*+Na]$^+$.

Compound 3b: TFA (7.00 g, 61.39 mmol) was added to a solution of **3a** (4.00 g, 12.26 mmol) in CH_2Cl_2 (30 mL) at 0 °C, and the mixture was stirred for 6 h before being quenched with an excess of methanol. Evaporation of the solvents in vacuo yielded the salt as a colorless solid (2.03 g, 100 %). ^{1}H NMR (D_2O): δ = 1.92–2.52 (m, 8H; CH_2), 3.31–3.72 (m, 7H; CH_2, OCH_3), 4.45–4.59 ppm (m, 2H; CH); ^{13}C NMR (75.5 MHz, D_2O): δ = 23.81, 24.48, 28.36, 28.64, 30.43, 46.76, 47.25, 47.40, 53.06, 59.01, 59.61, 107.11, 113.38, 119.17, 124.96, 162.36, 163.07, 168.19, 174.15 ppm; HRMS: *m*/*z*: calcd: 227.13 [*M*+H]$^+$; found: 227.1387 [*M*+H]$^+$.

Compound 3c: LiOH·H_2O (1.30 g, 31.00 mmol) was added to a solution of **3a** (5.00 g, 15.30 mmol) in methanol (50 mL) and water (20 mL) at −5 °C with stirring, and the reaction mixture was allowed to warm to room temperature. After the mixture had been stirred for 3 h, the solvents were evaporated in vacuo at room temperature. The residue was dissolved with ethyl acetate, and the pH value of the solution was adjusted carefully to around pH 5–6 with 10 % $KHSO_4$ aqueous solution. After the organic phase had been washed with brine and dried over $MgSO_4$, the crude product was purified by column chromatography (ethyl acetate/hexane 2:1) to afford colorless crystals (4.30 g, 90 %). ^{1}H NMR ($CDCl_3$): δ = 1.34, 1.40 (ds, 9H; Boc), 1.68–2.20 (m, 8H; CH_2), 3.33–3.75 (m, 4H; CH_2), 4.33–4.57 ppm (m, 2H; CH); ^{13}C NMR ($CDCl_3$): δ = 23.76, 24.29, 25.08, 28.05, 28.26, 28.47, 28.53, 28.55, 28.60, 29.30, 30.13, 46.82, 47.07, 47.10, 57.79, 57.89, 59.45, 59.55, 79.89, 79.98, 153.83, 154.82, 172.99, 173.31, 173.80, 174.16 ppm; HRMS: *m*/*z*: calcd: 313.17 [*M*+H]$^+$; found: 313.1760 [*M*+H]$^+$, 335.1580 [*M*+Na]$^+$, 351.1319 [*M*+K]$^+$.

Compound 3d: The acid **3c** (2.00 g, 6.40 mmol) and pentafluorophenol (1.80 g, 9.80 mmol) were dissolved in CH_2Cl_2 (30 mL) and stirred for 10 min. EDC (1.20 g, 6.40 mmol) was then added. The mixture was stirred overnight at room temperature before being washed with saturated $NaHCO_3$ and brine, successively. After the organic phase had been dried over $MgSO_4$, purification by column chromatography (ethyl acetate/hexane 2:1) afforded the product as colorless crystals (2.82 g, 92 %). ^{1}H NMR ($CDCl_3$): δ = 1.39, 1.43 (ds, 9H; Boc), 1.80–2.39 (m, 8H; CH_2), 3.35–3.86 (m, 4H; CH_2), 4.38–4.51 (m, 1H; CH), 4.48–4.90 ppm (m, 1H; CH); ^{13}C NMR ($CDCl_3$): δ = 23.65, 24.19, 25.23, 25.32, 28.53, 28.63, 29.03, 29.11, 29.26, 30.20, 46.63, 46.80, 47.01, 57.72, 57.83, 58.54, 79.71, 79.78, 136.97, 138.98, 140.18, 140.25, 142.19, 142.26, 153.73, 154.73, 168.37, 168.64, 171.65, 172.06 ppm; HRMS: *m*/*z*: calcd: 478.15 [*M*+H]$^+$; found: 379.1077 [*M*−Boc+H]$^+$, 479.1604 [*M*+H]$^+$, 501.1428 [*M*+Na]$^+$, 517.1170 [*M*+K]$^+$.

Compound 4a: A solution of **3b** (4.50 g, 13.25 mmol) and TEA (7.00 g, 69.15 mmol) in dry DMF (30 mL) was added dropwise to a solution of **3d** (4.35 g, 9.10 mmol) in dry DMF (30 mL) at room temperature. The mixture was stirred overnight and then washed with saturated $NaHCO_3$ and brine, successively. After the organic phase had been dried over $MgSO_4$, purification by column chromatography (CH_2Cl_2/methanol 20:1) afforded the product as colorless crystals (3.30 g, 70 %). ^{1}H NMR ($CDCl_3$): δ = 1.39, 1.44 (ds, 9H; Boc), 1.78–2.16 (m, 16H; CH_2), 3.36–3.82 (m, 11H; CH_2, OCH_3), 4.37–4.54 (m, 2H; CH), 4.69–4.75 ppm (m, 2H; CH); ^{13}C NMR ($CDCl_3$): δ = 23.80, 24.33, 24.80, 24.84, 24.97, 25.06, 28.02, 28.06, 28.18, 28.57, 28.68, 28.90, 29.22, 30.10, 46.64, 46.67, 46.84, 47.08, 47.11, 52.31, 57.89, 57.94, 58.00, 58.03, 58.10, 58.74, 79.52, 79.57, 153.98, 154.78, 170.32, 170.65, 170.76, 171.09, 171.66, 172.93, 172.97 ppm; HRMS:

m/z: calcd: 521.29 $[M+H]^+$; found: 421.2441 $[M-Boc+H]^+$, 521.2980 $[M+H]^+$, 543.2794 $[M+Na]^+$, 559.2539 $[M+K]^+$.

Compound 4b: TFA (2.50 g, 20.00 mmol) was added to a solution of **4a** (2.5 g, 4.80 mmol) in CH_2Cl_2 (50 mL) at 0 °C, and the mixture was stirred for 6 h before an excess amount of methanol was added to quench the reaction. Evaporation of the solvents in vacuo yielded the deprotected product as a colorless solid (2.56 g, 100 %). ^{1}H NMR (D_2O): δ = 1.77–2.49 (m, 16H; CH_2), 3.31–3.65 (m, 11H; CH_2, OCH_3), 4.31–4.53 ppm (m, 4H; CH); ^{13}C NMR (D_2O): δ = 23.92, 24.64, 24.67, 27.87, 28.01, 28.34, 28.70, 46.74, 47.45, 47.72, 47.80, 53.01, 58.75, 59.09, 59.19, 59.57, 115.26, 117.58, 162.90, 163.18, 167.72, 171.22, 172.10, 174.80 ppm; HRMS: *m/z*: calcd: 421.24 $[M+H]^+$; found: 421.2442 $[M+H]^+$, 443.2259 $[M+Na]^+$.

Compound 4c: $LiOH\cdot H_2O$ (1.00 g, 23.00 mmol) was added to a solution of **4a** (6.00 g, 11.50 mmol) in methanol (100 mL) and water (30 mL) at −5 °C with stirring, and the reaction mixture was allowed to warm to room temperature. After the mixture had been stirred for 3 h, the solvents were evaporated in vacuo at room temperature. The residue was dissolved in CH_2Cl_2, and the pH value of the solution was adjusted carefully to around pH 5–6 with 10 % $KHSO_4$ aqueous solution. After the organic phase had been washed with brine and dried over $MgSO_4$, purification by column chromatography (CH_2Cl_2/methanol 5:1) afforded the product as colorless crystals (4.09 g, 70 %). ^{1}H NMR ($CDCl_3$): δ = 1.34, 1.39 (ds, 9H; Boc), 1.77–2.08 (m, 16H; CH_2), 3.36–3.78 (m, 8H; CH_2), 4.24–4.45 (m, 2H; CH), 4.65–4.70 ppm (m, 2H; CH); ^{13}C NMR ($CDCl_3$): δ = 23.48, 23.80, 24.34, 24.91, 25.03, 27.83, 27.98, 28.14, 28.57, 28.66, 29.23, 29.78, 30.79, 45.37, 47.09, 49.65, 57.86, 58.01, 58.09, 79.54, 79.60, 153.91, 154.76, 170.87, 171.13 ppm; HRMS: *m/z*: calcd: 507.27 $[M+H]^+$; found: 407.2620 $[M-Boc+H]^+$, 507.2822 $[M+H]^+$, 529.2624 $[M+Na]^+$.

Compound 4d: The acid **4c** (3.40 g, 6.71 mmol) and pentafluorophenol (1.60 g, 8.69 mmol) were dissolved in CH_2Cl_2 (100 mL) and stirred for 10 min. EDC (1.50 g, 7.29 mmol) was then added. The reaction mixture was stirred overnight at room temperature before being washed with saturated $NaHCO_3$ and brine, successively. After the organic phase had been dried over $MgSO_4$, purification by column chromatography (CH_2Cl_2/methanol 10:1) afforded the product as colorless crystals (3.88 g, 86 %). ^{1}H NMR ($CDCl_3$): δ = 1.36, 1.41 (ds, 9H; Boc), 1.79–2.33 (m, 16H; CH_2), 3.35–3.79 (m, 8H; CH_2), 4.36–4.82 ppm (m, 4H; CH); ^{13}C NMR ($CDCl_3$): δ = 23.78, 24.32, 24.73, 24.77, 24.93, 25.08, 28.07, 28.24, 28.54, 28.64, 28.86, 29.06, 29.22, 30.10, 46.63, 46.66, 46.80, 47.01, 47.07, 57.76, 57.85, 57.91, 58.02, 58.46, 58.68, 79.44, 79.50, 136.96, 138.95, 140.14, 142.12, 153.89, 154.72, 168.50, 170.40, 170.70, 171.00, 171.60 ppm; HRMS: *m/z*: calcd: 673.26 $[M+H]^+$; found: 573.2121 $[M-Boc+H]^+$, 673.2683 $[M+H]^+$, 695.2460 $[M+Na]^+$, 711.2235 $[M+K]^+$.

Compound 5: A solution of **4b** (3.05 g, 5.71 mmol) and DiPEA (5.20 g, 40.14 mmol) in dry DMF (20 mL) was added dropwise to a solution of **4d** (3.20 g, 4.76 mmol) in dry DMF (30 mL) at room temperature. After the reaction mixture had been stirred overnight, it was washed successively with saturated $NaHCO_3$ and brine. The organic phase was dried with $MgSO_4$. Purification by column chromatography (CH_2Cl_2/MeOH 20:1) afforded **5** as colorless crystals (3.20 g, 74 %). ^{1}H NMR ($CDCl_3$): δ = 1.36, 1.41 (ds, 9H; Boc), 1.78–2.08 (m, 32H; CH_2), 3.35–3.77 (m, 19H; CH_2, CH_3), 4.35–4.47 (m, 2H; CH), 4.68 ppm (brs, 6H; CH); ^{13}C NMR ($CDCl_3$): δ = 23.78, 24.31, 24.65, 24.72, 24.77, 24.81, 24.85, 24.90, 25.09, 27.94, 27.99, 28.05, 28.21, 28.56, 28.67, 28.84, 29.20, 30.11, 46.55, 46.80, 46.86, 46.97, 47.01, 47.07, 47.16, 52.29, 57.86, 57.92, 58.01, 58.65, 79.38, 79.45, 153.90, 154.74, 170.19, 170.26, 170.51, 170.60, 170.88, 171.48, 172.90 ppm; HRMS: *m/z*: calcd: 908.50 $[M+H]^+$; found: 931.4917 $[M+Na]^+$, 947.4630 $[M+K]^+$.

Compound 6: $NaBH_4$ (0.29 g, 7.66 mmol) and LiCl (0.48 g, 11.48 mmol) were added to a solution of **5** (2.32 g, 2.55 mmol) in dry THF (50 mL) at −5 °C. After the reaction mixture had been stirred for 3 h, it was allowed to warm to room temperature and was stirred for another 24 h. Water was added to quench the reaction, and the solvents were evaporated in vacuo. The residue was dissolved in CH_2Cl_2 and washed with saturated $NaHCO_3$ and brine, successively. After the organic phase had been dried over $MgSO_4$, purification by column chromatography (CH_2Cl_2/MeOH 10:1) afforded **6** as a colorless solid (1.80 g, 80 %). ^{1}H NMR ($CDCl_3$): δ = 1.31, 1.36 (ds, 9H; Boc), 1.49–2.04 (m, 32H; CH_2), 3.31–3.65 (m, 19H; CH, CH_2), 4.00–4.42 (m, 2H; CH), 4.64 (brs, 6H; CH), 4.88–4.98 ppm (m, 1H; OH); ^{13}C NMR ($CDCl_3$): δ = 22.16, 23.58, 24.12, 24.42, 24.58, 24.63, 24.75, 24.90, 25.06, 27.43, 27.58, 27.75, 27.86, 28.03, 28.37, 28.49, 28.59, 28.70, 29.01, 29.28, 29.91, 45.70, 46.66, 46.84, 47.37, 47.45, 57.68, 57.75, 57.84, 57.91, 58.45, 59.69, 60.70, 66.34, 66.70, 79.20, 79.26, 153.72, 154.54, 170.10, 170.19, 170.35, 170.73, 170.98, 171.13, 171.31, 172.98 ppm; HRMS: *m/z*: calcd: 880.51 $[M+H]^+$; found: 881.5103 $[M+H]^+$, 903.4967 $[M+Na]^+$, 919.4731 $[M+K]^+$.

Compound 7: A solution of trimethylacetyl chloride (0.16 g, 1.35 mmol) in dry THF (5 mL) was added dropwise into a mixture of **6** (0.40 g, 0.45 mmol), TEA (0.23 g, 2.25 mmol), and DMAP (0.1 g) in dry THF (20 mL) at 0 °C over a period of 15 min. After the reaction mixture had been stirred for 4 h at room temperature, it was washed with saturated $NaHCO_3$ and brine, successively. The organic phase was dried over $MgSO_4$. Evaporation of the solvents under vacuum, followed by chromatographic separation (CH_2Cl_2/CH_3OH 20:1), yielded **7** as a colorless solid (0.37 g, 86 %). ^{1}H NMR ($CDCl_3$): δ = 1.28 (s, 9H; CH_3), 1.38, 1.42 (ds, 9H; Boc), 1.78–2.08 (m, 32H; CH_2), 3.35–3.81 (m, 16H; CH_2), 4.11–4.72 ppm (m, 10H; CH); ^{13}C NMR ($CDCl_3$): δ = 23.77, 24.31, 24.53, 24.61, 24.78, 24.80, 24.86, 25.11, 27.16, 27.40, 27.41, 27.96, 28.01, 28.06, 28.22, 28.57, 28.70, 28.86, 29.23, 30.11, 31.59, 46.81, 46.89, 47.05, 47.10, 47.16, 55.79, 57.84, 57.92, 58.02, 58.06, 62.14, 79.40, 79.49, 153.91, 154.70, 170.24, 170.26, 170.55, 170.83, 170.90, 171.50, 177.71 ppm; HRMS: *m/z*: calcd: 965.56 $[M+H]^+$; found: 965.5460 $[M+H]^+$, 987.5321 $[M+Na]^+$.

Compound 8: Compound **7** (0.20 g) in TFA (8 mL) was stirred at room temperature for 5 h, and then MeOH (20 mL) was added to quench the reaction. After evaporation of the solvents, the deprotected sample was dialyzed against pure water for 3 days. This was followed by freeze drying, which afforded compound **8** as a colorless solid (0.21 g, 100 %). ^{1}H NMR (D_2O): δ = 1.29 (s, 9H; CH_3), 1.79–2.10 (m, 32H; CH_2), 3.36–3.83 (m, 16H; CH_2), 4.12–4.74 ppm (m, 10H; CH); ^{13}C NMR (D_2O): δ = 23.79, 24.32, 24.53, 24.65, 24.76, 24.82, 24.84, 25.13, 27.42, 27.94, 29.26, 30.15, 31.56, 44.71, 44.73, 44.75, 46.78, 46.87, 55.76, 57.87, 57.96, 58.04, 58.11, 62.15, 79.43, 79.48, 153.94, 154.73, 170.20, 170.28, 170.56, 170.83, 170.95, 171.50, 176.42, 176.45, 177.73 ppm; HRMS: *m/z*: calcd: 865.52 $[M+H]^+$; found: 865.5180 $[M+H]^+$, 887.5112 $[M+Na]^+$.

Compound 1: A solution of MAC (0.53 g, 5.11 mmol) in THF (20 mL) was added dropwise into a mixture of **6** (1.50 g, 1.70 mmol), triethylamine (TEA; 1.03 g, 10.21 mmol), and dimethylaminopyridine (DMAP; 0.02 g) in dry THF (30 mL) at 0 °C over a period of 30 min. After the reaction mixture had been stirred for 4 h at room temperature, it was washed with saturated $NaHCO_3$ and brine, successively. The organic phase was dried over $MgSO_4$. Evaporation of the solvents under vacuum at room temperature, followed by chromatographic separation (CH_2Cl_2/CH_3OH 20:1) yielded **1** as a colorless solid (1.29 g, 80 %). ^{1}H NMR ($CDCl_3$): δ = 1.38, 1.42 (ds, 9H; Boc), 1.77–2.08 (m, 35H; CH_2, CH_3), 3.35–3.80 (m, 16H; CH_2), 4.10–4.74 (m, 10H; CH, CH_2), 5.57 (s, 1H; CH), 6.07 ppm (s, 1H; CH); ^{13}C NMR ($CDCl_3$): δ = 18.49, 23.79, 24.32, 24.52, 24.60, 24.76, 24.82, 24.86, 25.10, 27.15, 27.96, 28.00, 28.06, 28.22, 28.57, 28.68, 28.84, 29.21, 30.12, 31.58, 46.78, 46.89, 47.02, 47.08, 47.18, 55.79, 57.87, 57.94, 58.02, 58.08, 64.04, 79.41, 79.48, 125.78, 136.29, 153.92, 154.76, 167.24, 170.22, 170.28, 170.54, 170.81, 170.92, 171.51 ppm; HRMS: *m/z*: calcd: 948.53 $[M+H]^+$; found: 949.5420 $[M+H]^+$, 971.5217 $[M+Na]^+$.

Poly(1): Macromonomer **1** (0.3–0.5 g) and AIBN (0.5 wt % based on the macromonomer) in the appropriate solvent (0.8 mL) inside a Schlenk tube were degassed by several freeze–pump–thaw cycles and were then kept at 60 °C with stirring for a predetermined time. The polymerization was stopped by cooling, and the polymer was dissolved in CH_2Cl_2 and purified by column chromatography (silica gel with CH_2Cl_2 as the eluent). GPC results are shown in Table 1; ^{1}H NMR ([D_6]DMSO, 80 °C): δ = 0.85 (brs; CH_3), 0.92 (brs; CH_3), 1.21 (brs; CH_3), 1.34 (brs; CH_3), 1.86 (brs; CH_2), 2.12 (brs; CH_2), 3.25–3.63 (m; CH, CH_2), 4.38 (brs; CH), 4.58 ppm (brs; CH); ^{13}C NMR ([D_6]DMSO, 80 °C): δ = 9.25, 24.89, 27.98, 28.79, 46.92, 47.13, 58.10, 67.06, 70.58, 73.02, 78.89, 170.07 ppm.

De-poly(1): Poly(**1**) (0.20 g) in TFA (5 mL) was stirred overnight at room temperature, and then MeOH (10 mL) was added to quench the reaction. After evaporation of the solvents, the deprotected polymer was dialyzed against pure water for 10 days. This was followed by freeze drying, which

afforded the de-poly(**1**) as a colorless solid foam. ^{1}H NMR ([D$_6$]DMSO, 80 °C): δ = 0.85 (brs; CH$_3$), 0.95 (brs; CH$_3$), 0.98 (brs; CH$_3$), 1.26–1.29 (m; CH$_3$), 1.88 (brs; CH$_2$), 2.12 (brs; CH$_2$), 3.44–3.70 (m; CH, CH$_2$), 4.14 (brs; CH), 4.49–4.66 ppm (m; CH); no resolved carbon NMR spectrum was achieved.

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[1] a) Y. Okamoto, E. Yashima, C. Yamamoto in *Materials-Chirality* (Eds.: M. M. Green, R. J. M. Nolte, E. W. Meijer), Wiley, New York, **2003**, pp. 157–208; b) J. W. Lockman, N. M. Paul, J. R. Parquette, *Prog. Polym. Sci.* **2005**, *30*, 423–452; c) D. B. Amabilino, J. Veciana, *Top. Curr. Chem.* **2006**, *265*, 253–302; d) D. A. Leigh, E. M. Pérez, *Top. Curr. Chem.* **2006**, *265*, 185–208.

[2] a) Y. Okamoto, T. Nakano, *Chem. Rev.* **1994**, *94*, 349–372; b) T. Nakano, Y. Okamoto, *Chem. Rev.* **2001**, *101*, 4013–4038; c) J. J. L. M. Cornelissen, A. E. Rowan, R. J. M. Nolte, N. A. J. M. Sommerdijk, *Chem. Rev.* **2001**, *101*, 4039–4070; d) M. M. Green, K.-S. Cheon, S.-Y. Yang, J.-W. Park, S. Swansburg, W. Liu, *Acc. Chem. Res.* **2001**, *34*, 672–680; e) E. Yashima, K. Maeda, T. Nishimura, *Chem. Eur. J.* **2004**, *10*, 42–51; f) J. G. Rudick, V. Percec, *New J. Chem.* **2007**, *31*, 1083–1096.

[3] a) A. R. A. Palmans, E. W. Meijer, *Angew. Chem.* **2007**, *119*, 9106–9126; *Angew. Chem. Int. Ed.* **2007**, *46*, 8948–8968; b) H.-J. Kim, Y.-B. Lim, M. Lee, *J. Polym. Sci. Part A Polym. Chem.* **2008**, *46*, 1925–1935; c) G. A. Hembury, V. V. Borovkov, Y. Inoue, *Chem. Rev.* **2008**, *108*, 1–73.

[4] E. Yashima, K. Maeda, *Macromolecules* **2008**, *41*, 3–12.

[5] T. Nakano, Y. Okamoto, *Macromol. Rapid Commun.* **2000**, *21*, 603–612.

[6] a) J. Bella, M. Eaton, B. Brodsky, H. M. Berman, *Science* **1994**, *266*, 75–81; b) S. K. Holmgren, K. M. Taylor, L. E. Bretscher, R. T. Raines, *Nature* **1998**, *392*, 666–667; c) A. V. Persikov, J. A. Ramshaw, A. Kirkpatrick, B. Brodsky, *Biochemistry* **2000**, *39*, 14960–14967; d) A. V. Persikov, J. A. M. Ramshaw, A. Kirkpatrick, B. Brodsky, *J. Am. Chem. Soc.* **2003**, *125*, 11500–11501; e) M. Kohtani, T. C. Jones, J. E. Schneider, M. F. Jarrold, *J. Am. Chem. Soc.* **2004**, *126*, 7420–7421; f) M. D. Shoulders, J. A. Hodges, R. T. Raines, *J. Am. Chem. Soc.* **2006**, *128*, 8112–8113; g) S. Rele, Y. Song, R. P. Apkarian, Z. Qu, V. P. Conticello, E. L. Chaikof, *J. Am. Chem. Soc.* **2007**, *129*, 14780–14787; h) V. Gauba, J. D. Hartgerink, *J. Am. Chem. Soc.* **2007**, *129*, 15034–15041; i) F. W. Kotch, I. A. Guzei, R. T. Raines, *J. Am. Chem. Soc.* **2008**, *130*, 2952–2953; j) N. Dai, X. J. Wang, F. A. Etzkorn, *J. Am. Chem. Soc.* **2008**, *130*, 5396–5397; k) D. Diana, B. Ziaco, G. Colombo, G. Scarabelli, A. Romanelli, C. Pedone, R. Fattorusso, L. D. D'Andrea, *Chem. Eur. J.* **2008**, *14*, 4164–4166.

[7] a) P. M. Cowan, S. Mcgavin, *Nature* **1955**, *176*, 501–503; b) W. Traub, U. Shmueli, *Nature* **1963**, *198*, 1165–1166.

[8] a) R. Z. Dramer, L. Vitagliano, J. Bella, R. Berisio, L. Mazzarella, B. Brodsky, A. Zagari, H. M. Berman, *J. Mol. Biol.* **1998**, *280*, 623–638; b) J. T. Nguyen, C. W. Turck, F. E. Cohen, R. N. Zuckermann, W. A. Lim, *Science* **1998**, *282*, 2088–2092; c) Z. Shi, K. Chen, Z. Liu, N. R. Kallenbach, *Chem. Rev.* **2006**, *106*, 1877–1897.

[9] a) M. P. Williamson, *Biochem. J.* **1994**, *297*, 249–260; b) D. S. Daniels, A. Schepartz, *J. Am. Chem. Soc.* **2007**, *129*, 14578–14579.

[10] a) J. Kurtz, A. Berger, E. Katchalski, *Nature* **1956**, *178*, 1066–1067; b) I. Z. Steinberg, W. F. Harriugton, A. Berger, M. Sela, E. Katchalski, *J. Am. Chem. Soc.* **1960**, *82*, 5263–5279; c) J. Engel, G. Schwarz, *Angew. Chem.* **1970**, *82*, 468–479; *Angew. Chem. Int. Ed. Engl.* **1970**, *9*, 389–400; d) M. Mutter, T. Wöhr, S. Gioria, M. Kellar, *Biopolymers* **1999**, *51*, 121–128.

[11] a) A. R. Downie, A. A. Randall, *Trans. Faraday Soc.* **1959**, *55*, 2132–2140; b) F. Gornick, L. Mandelkern, A. F. Diorio, D. E. Roberts, *J. Am. Chem. Soc.* **1964**, *86*, 2549–2555; c) J. Engel, *Biopolymers* **1966**, *4*, 945–948.

[12] a) C. M. Deber, F. A. Bovey, J. P. Carver, E. R. Blout, *J. Am. Chem. Soc.* **1970**, *92*, 6191–6198; b) D. A. Torchia, F. A. Bovey, *Macromolecules* **1971**, *4*, 246–251; c) D. E. Dorman, F. A. Bovey, *J. Org. Chem.* **1973**, *38*, 2379–2383; d) Y.-Y. Chao, R. Bersohn, *Biopolymers* **1978**, *17*, 2761–2767.

[13] a) H. Okabayashi, T. Isemura, S. Sakakibara, *Biopolymers* **1968**, *6*, 323–330; b) N. Helbecque, M. H. Loucheux-Lefebvre, *Int. J. Pept. Protein Res.* **1982**, *19*, 94–101; c) F. Rabanal, M. D. Ludevid, M. Pons, E. Giralt, *Biopolymers* **1993**, *33*, 1019–1028; d) R. K. Dukor, T. A. Keiderling, *Biospectroscopy* **1996**, *2*, 83–100.

[14] J.-C. Horng, R. T. Raines, *Protein Sci.* **2006**, *15*, 74–83.

[15] M. Kümin, L.-S. Sonntag, H. Wennemers, *J. Am. Chem. Soc.* **2007**, *129*, 466–467.

[16] S. Kakinoki, Y. Hirano, M. Oka, *Polym. Bull.* **2005**, *53*, 109–115.

[17] a) M. Y. Ogawa, J. F. Wishart, Z. Young, J. R. Miller, S. S. Isied, *J. Phys. Chem.* **1993**, *97*, 11456–11463; b) D. G. McCaffery, C. A. Slate, B. M. Nakhle, *Tetrahedron* **1995**, *51*, 9859–9872; c) D. G. McCaffery, D. A. Friesen, E. Danielson, *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 8200–8204; d) C. A. Slate, R. A. Binstead, T. J. Meyer, B. W. Erickson, *Lett. Pept. Sci.* **1999**, *6*, 61–69; e) D. R. Striplin, S. Y. Reece, D. G. McCaffery, C. G. Wall, D. A. Friesen, B. W. Erickson, T. J. Meyer, *J. Am. Chem. Soc.* **2004**, *126*, 5282–5291; f) S. A. Serron, W. Aldridge, C. N. Fleming, R. M. Danell, M. Sykora, M. Baik, D. M. Dattelbaum, T. J. Meyer, *J. Am. Chem. Soc.* **2004**, *126*, 14506–14514; g) W. S. Aldridge, B. J. Hornstein, S. Serron, D. M. Dattelbaum, J. R. Schoonover, T. J. Meyer, *J. Org. Chem.* **2006**, *71*, 5186–5190.

[18] a) L. Crespo, G. Sanclimens, B. Montaner, R. Pérez-Tomás, M. Royo, M. Pons, F. Albericio, E. Giralt, *J. Am. Chem. Soc.* **2002**, *124*, 8876–8883; b) G. Sanclimens, L. Crespo, E. Giralt, F. Albericio, M. Royo, *J. Org. Chem.* **2005**, *70*, 6274–6281.

[19] M. Zhang, A. H. E. Müller, *J. Polym. Sci. Part A Polym. Chem.* **2005**, *43*, 3461–3481.

[20] For polymer bottlebrushes with polydispersed peptide side chains, see, for example: a) B. Zhang, K. Fischer, M. Schmidt, *Macromol. Chem. Phys.* **2005**, *206*, 157–162; b) L. Zhang, W. Li, A. Zhang, *Prog. Chem.* **2006**, *18*, 939–949; c) T. Waku, M. Matsusaki, T. Kaneko, M. Akashi, *Macromolecules* **2007**, *40*, 6385–6392; d) N. Gunari, Y. Cong, B. Zhang, K. Fischer, A. Janshoff, M. Schmidt, *Macromol. Rapid Commun.* **2008**, *29*, 821–825.

[21] a) A. Zhang, A. D. Schlüter, *Chem. Asian J.* **2007**, *2*, 1540–1548; b) A. Zhang, F. Rodríguez-Ropero, D. Zanuy, C. Alemán, E. W. Meijer, A. D. Schlüter, *Chem. Eur. J.* **2008**, *14*, 6924–6934.

[22] Macromonomer **1** adopts different helical conformations in isopropanol/acetonitrile (1:1) and HFIP, and this difference was expected to indicate different steric effects in the polymerization process. For the corresponding CD spectra of macromonomer **1**, see Figure S1 in the Supporting Information.

[23] A. Zhang, B. Zhang, E. Wächtersbach, M. Schmidt, A. D. Schlüter, *Chem. Eur. J.* **2003**, *9*, 6083–6092.

[24] HFIP was reported to show effects on polymer-backbone tacticity in radical polymerizations, see, for example: a) Y. Isobe, K. Yamada, T. Nakano, Y. Okamoto, *Macromolecules* **1999**, *32*, 5979–5981; b) Y. Isobe, K. Yamada, T. Nakano, Y. Okamoto, *J. Polym. Sci. Part A Polym. Chem.* **2000**, *38*, 4693–4703; c) Y. Miura, T. Satoh, A. Narumi, O. Nishizawa, Y. Okamoto, T. Kakuchi, *Macromolecules* **2005**, *38*, 1041–1043; d) Y. Miura, T. Satoh, A. Narumi, O. Nishizawa, Y. Okamoto, T. Kakuchi, *J. Polym. Sci. Part A Polym. Chem.* **2006**, *44*, 1436–1446.

[25] K. Hatada, T. Kitayama, K. Ute, *Prog. Polym. Sci.* **1988**, *13*, 189–276.

[26] Polymer bottlebrushes can adopt either a cylindrical shape when the main-chain length (L_m) is much longer than the side-chain length (L_s) or a spherical shape when the ratio of L_m/L_s is relatively small. We propose that the stable PPII conformation in the present case would only remain for the cylindrical bottlebrushes, in which all of the side chains are aligned in parallel to form the overcrowded structures. For reports regarding bottlebrush shapes, see, for example: a) Y. Tsukahara, K. Tsutsumi, Y. Yamashita, S. Shimada, *Macromolecules* **1990**, *23*, 5201–5208; b) M. Wintermantel, M. Gerle, K. Fischer, M. Schmidt, I. Wataoka, H. Urakawa, K. Kajiwara, Y. Tsukahara, *Macromolecules* **1996**, *29*, 978–983; c) P. Dziezok, K. Fischer, M. Schmidt, S. S. Sheiko, M. Möller, *Angew. Chem.* **1997**, *109*, 2894–2897; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2812–2815; d) K. Fischer, M. Schmidt, *Macromol. Rapid Commun.* **2001**, *22*, 787–791; e) S. Rathgeber, T. Pakula, A. Wilk, K. Matyjaszewski, K. L. Beers, *J. Chem. Phys.* **2005**, *122*, 124904/1–124904/13.

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