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Synthesis of Dendronized Polymers by a "n + 2" Approach

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S *Supporting Information*

ABSTRACT: A series of dendronized polymers (DP) were synthesized by attaching second-generation dendron onto the preformed DP core of generation 1−3 (n + 2 approach). The obtained DP were compared to the reference DP prepared by the conventional graft-from (n + 1) approach using GPC, UV−vis, ^{1}H NMR, and AFM analyses. The former two analyses showed that the newly prepared DP tend to have a more significant decrease in dendron integrity as the generation increases; however, the striking similarities from the latter two analyses suggest that the properties of the new samples do not much deviate from the reference DP by the graft-from approach. The advantages of the "n + 2" approach over the "n + 1" approach include shorter reaction time, higher yield, and easier purification. On top of these, it has the power of surpassing some selected postpolymerization steps, which are required for the conventional graft-from approach and may be detrimental in some occasions.
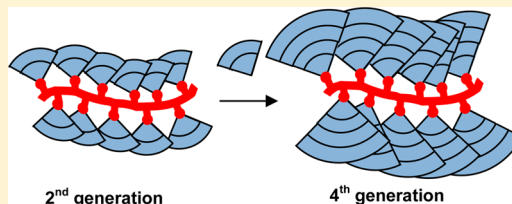
1. INTRODUCTION

Dendronized polymers constitute a unique class of macromolecules in which the linear backbone carries dendritic wedges (dendrons).[1−12] Based on the order of backbone formation and dendron attachments, syntheses of DP are conventionally categorized into three types: macromonomer, graft-from, and graft-to approaches (Figure 1a−c).[8] The macromonomer approach includes the preparation and
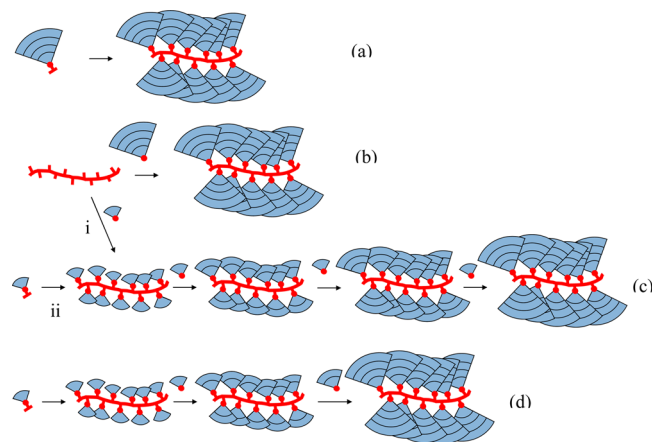

Figure 1. Schematic illustration of the synthetic strategies for DP of the fourth generation: (a) macromonomer approach, (b) graft-to approach, (c) graft-from approach, and (d) "n + 2" hybrid approach. In a strict sense, by the graft-from approach, the polymer backbone should be generated before the introduction of G1 dendron (i), but for convenience, it is also very frequently produced by the polymerization of G1 monomer (ii). This modified version of the graft-from approach was intensively studied in our group and is also the basis of the "n + 2" hybrid approach.

polymerization of a dendron carrying a polymerizable group at its focal point. By this approach, the backbone is constructed in the last step, so postpolymerization reaction is avoided, which simplifies the isolation and purification of the resulting DP. Moreover, every backbone repeat unit of the resulting DP carries a structurally perfect dendron, which cannot be achieved by the other approaches. The main disadvantage of this approach stems from the steric effect of the high generation macromonomers (g > 3), which normally hinders the polymerization.[13] Therefore, long chain DP of high generations are normally synthesized by the other two approaches, which include the construction of the backbone through polymerization of small monomers, followed by the attachment of dendrons using postpolymerization reactions. Therefore, the chain length and chain length distribution can be controlled by polymerization methods, and it is convenient to obtain a long linear backbone. A common disadvantage of these two approaches is the inevitable incompletion of the dendronizations because the postpolymerization modification requires a large number of simultaneous reactions on the same molecule. As a result, any DP synthesized by these two approaches would carry either defective dendrons (by graft-from approach) or no dendron (by graft-to approach) on some main chain repeat units. These two approaches differ in the fashion of dendron attachment. By the graft-to approach, the dendron at the desired generation (g > 1) is attached onto the backbone directly. By the graft-from approach, the dendrons are constructed in a step-by-step fashion by grafting the smallest dendritic unit (first-generation dendron, G1 dendron, or DG1) repeatedly from the backbone. This approach is usually

Scheme 1. Synthesis of *h*PG4 from *de*PG2 by "*n* + 2" and PG4 by Graft-From ("*n* + 1") Approaches[a]
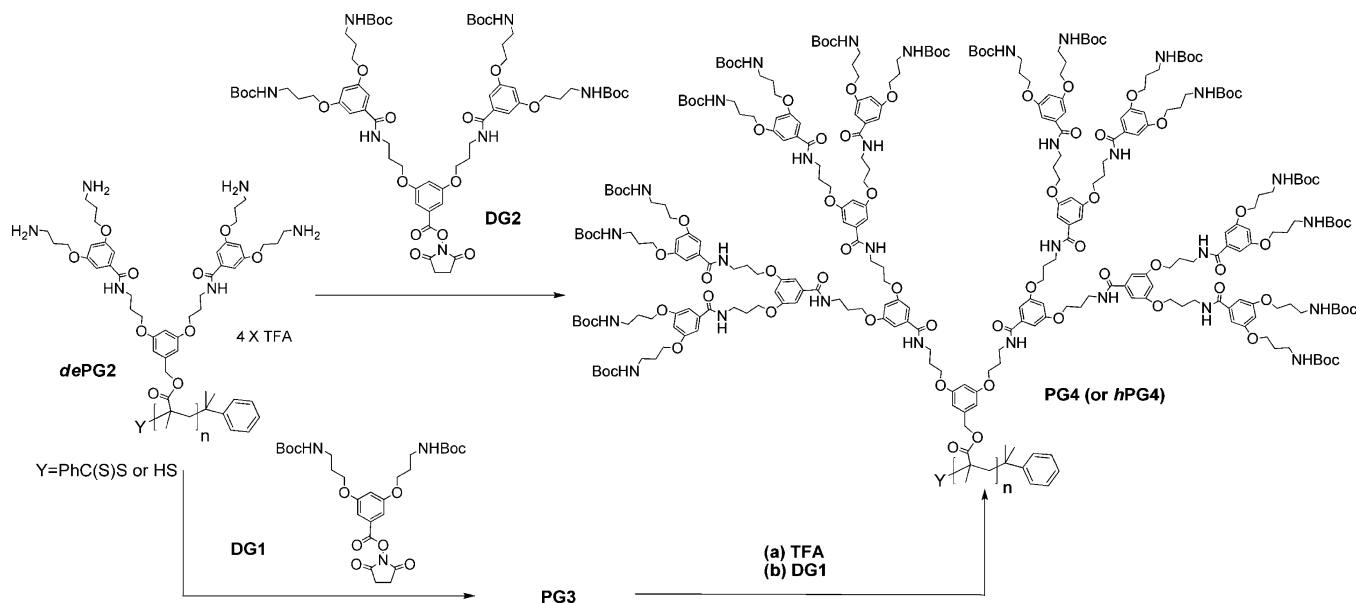
[a]*h***PG4** and **PG4** have the same chemical structure. Polymer backbone (carrying G1 dendron) was synthesized according to a RAFT protocol. The polymers initially contain a dithiobenzoate at the main chain ends, which was largely converted into thiol subsequently, as shown by the end-group analysis using ^{1}H NMR spectroscopy (see Supporting Information).

accompanied by repeated deprotections of the functional groups on the DP "surface" prior to any further dendronizations. In general, the graft-from approach is superior with respect to the conversion of dendronization (usually quantified as the dendron coverage) because of the smaller size of the G1 dendron. It is therefore in DP syntheses more frequently employed than the graft-to approach. Recently, we have reported that ∼97% conversion was achieved in the dendronization of the amino groups on the surface of a fourth-generation DP with ∼170 000 amino groups.[14] Despite this feat, the graft-from approach usually suffers from long reaction time (∼10−35 days for each dendronization step), difficulty in the purification, and low overall yields. One seemingly good solution to these issues is the graft-to approach, by which all of the postpolymerization reactions are condensed into one step, so that the entire synthesis is shortened. However, in reality the attachment of large dendrons (*g* > 3) onto the backbone is so far not commonly an ideal option because the significant sacrifice in the structural integrity may greatly change the physical and chemical nature of the resulting DP, and therefore the products would be unacceptable.[15] If the size of the attachments is restricted to a "medium" level (such as a second-generation dendron **DG2**), the synthesis will still be shorter, while the steric hindrance may not be so large yet to cause a sharp decrease in the structural integrity (Figure 1d). Thus, the products may still remain acceptable. This approach is considered the hybrid between the graft-to and graft-from approaches and combines the advantages of both.

The idea of constructing dendritic structures using "medium" generation dendron units first appeared in the synthesis of dendrons and dendrimers. Moore and Wilkins et al. reported a double-exponential dendrimer growth based on an AB2-type monomer with orthogonally protected A and B functionalities.[16] The same strategy was also reported by Fréchet,[17] Sharpless,[18] Roy,[19] Stoddart,[20] and Schlüter.[13c,21] If a dendron prepared by this method is equipped with a polymerizable unit at its focal point, it can be polymerized to produced DP.[13c,21]

Despite the use of "medium" sized dendron units, this method is conceptually included in the macromonomer approach, so it also suffers from the same issues. Another conceptually different approach consisting of grafting medium generation dendrons directly onto DP cores was reported by our group, which is considered a true hybrid between graft-to and graft-from approaches. It involves the attachment of second-generation dendrons onto a second-generation DP core, producing a DP of the fourth generation in 83−93% chemical yield with ∼94% dendron coverage, as quantified by UV−vis spectroscopic measurements.[22] Similarly, by grafting a slightly modified G2 dendron onto a G1 backbone, a third-generation DP was produced in 93% yield.[23] The structural integrity of the resulting G3 DP was examined by analyzing the ^{1}H NMR spectrum of the G3 dendron after it was quantitatively cleaved off the backbone. The results suggested that the structural defects were too small in quantity to be detected by ^{1}H NMR spectroscopy. No further quantification was performed. Similar ideas were employed by Fréchet et al. in the synthesis of doubly dendronized linear polymers of the fifth and pseudo-sixth generations by attaching G3 Fréchet-type dendrons onto the preformed G2 and G3 DP cores.[15c] The highly efficient click chemistry guaranteed the efficiency of the reactions, as evidenced by GPC and NMR analyses. However, the yields of these reactions are low (44% for G5 and 10% for G6), and the exact structure perfections were not quantified. These early investigations seemed promising; however, due to the great success of the graft-from approach at the same time, these alternative approaches were not thoroughly studied.

Recently, we have encountered an unexpected chain scission during the acidic treatment of a fifth-generation DP to remove the Boc protecting groups and convert it into its charged counterpart.[24] This phenomenon hinders the further growth of DP toward higher generations by the conventional graft-from approach. Therefore, the "*n* + 2" approach, which has the potential to circumvent the use of the fifth generation, was investigated by attaching a second-generation active ester

dendron (**DG2**) onto the lower generation DP core. The resulting polymers are named *h***PG***n*, with the prefix *h* denoting "synthetical hybrid", which is used to distinguish it from those DP synthesized by conventional graft-from approach,[25] which are named **PG***n* with *n* being the generation number. Note that the concept "hybrid" here only refers to the synthetic methodology but not the chemical structure of DP, which is homogeneous. We in this paper report the synthesis of a homologous series of DP from the third to the fifth generation by this method. High-generation DP (*h***PG3−5**) were synthesized with high overall yields in shorter reaction times. (As an example, the synthesis of *h***PG4** is shown in Scheme 1.) They were characterized and carefully compared to the corresponding **PG3−5** from the "*n* + 1" (graft-from) approach as reference samples. The dendron coverages of *h***PG3−5** are generally lower yet still satisfying, as qualitatively suggested by GPC analyses and determined quantitatively by the UV−vis amplification method.[22] *h***PG3−5** and **PG3−5** did not show significant difference by AFM and ¹H NMR analyses. These facts demonstrate the power of the "*n* + 2" approach in the synthesis of high-generation DP. In the future, this method will be applied to synthesize *h***PG6** to avoid the chain degradation step at the fifth-generation level and may also be extended in the fashion of "*n* + 3", which may effectively produce DP of unprecedented generations.

2. RESULTS AND DISCUSSION

2.1. Synthetic Aspects. Starting polymer **PG1** was prepared according to the published procedure by reversible addition−fragmentation chain transfer (RAFT) protocol.[26] Number-average degree of polymerization (P_n) and the polydispersity index (PDI) of **PG1** are determined by GPC in DMF as ∼500 and ∼1.8, respectively. This is the common starting material for all higher generations (**PG2−5**, *de***PG1−4**, and *h***PG3−5**), which thus have a nearly constant P_n (∼500) and PDI (1.8−2.0). Charged DP (*de***PG1−4**) were synthesized by treating neutral **PG1−4** with neat trifluoroacetic acid (TFA) at −10 °C to remove the *tert*-butyloxycarbonyl (Boc) protecting groups quantitatively.[27] *h***PG3−5** were synthesized by attaching **DG2** onto *de***PG1−3** by Merrifield-type amidation (for example, see Scheme 1).[28] **DG2** was added in one portion that totally amounts for 3 equiv of **DG2** per amine group. Finally, the reaction mixture was precipitated from diethyl ether and purified by column chromatography using silica gel as the stationary phase and dichloromethane as eluent, followed by lyophilization from 1,4-dioxane to yield powder-like DP products *h***PG3−5**. The yields are inversely correlated with the generations, typically in the range of 65−73% (Table 1), which are ∼5−12% higher than the overall yields of two dendronizations by the "*n* + 1" approach for the same conversions. Besides having better yields, the "*n* + 2" approach is also remarkably shorter than the graft-from approach by ∼3−5 weeks because of the condensation of the two extra steps (dendronization and deprotection, see Scheme 1).

2.2. Comparison of the DP by "*n* + 2" and "*n* + 1" Approaches. Compared to the conventional "*n* + 1" approach, the "*n* + 2" approach obviously has the advantages of being shorter and easier to handle, which also lead to higher yields. However, this method can only be considered beneficial if the dendron integrity is retained. It is therefore important to compare the obtained products (*h***PG3−5**) to those reference samples **PG3−5** from the conventional approach. A rough solubility test of *h***PG3−5** showed that they are well soluble in

Table 1. Yields and Coverages for the Dendronization Reactions[a]

generation (*n*)	"*n* + 2" approach (*h***PG***n*)		"*n* + 1" approach (**PG***n*)	
	yield (%)	coverage (%)	yield (%)	coverage (%)
3	73	99.7	66	99.7
4	68	98.8	63	99.8
5	65	93.5	53	99.7

[a]Regarding the "*n* + 2" approach, listed data refer to the last step (dendronization) in the synthesis. Regarding the "*n* + 1" approach, the yields data refer to the overall yields of the last two dendronization steps, so they can be directly compared to the yields for the "*n* + 2" approach. The coverage data for the "*n* + 1" approach refer only to the last dendronization step. Note that some previously generated amine defects may be dendronized in the later transformations (in a sense "fixed"); the listed coverage data may not exactly reflect the total amount of defects ever created in the transformation history from generation *n* − 2 to generation *n*. Therefore, it is in some sense not accurate to directly compare the coverages by the two approaches. This comparison was nevertheless performed because every dendronization step in the "*n* + 1" approach is almost quantitative, which means that defects from the earlier transformation are negligible (≤0.3%).

common organic solvents with no obvious difference from **PG3−5**. Solutions of *h***PG3−5** were measured by GPC and ¹H NMR (Figure 2) and compared to those of the reference
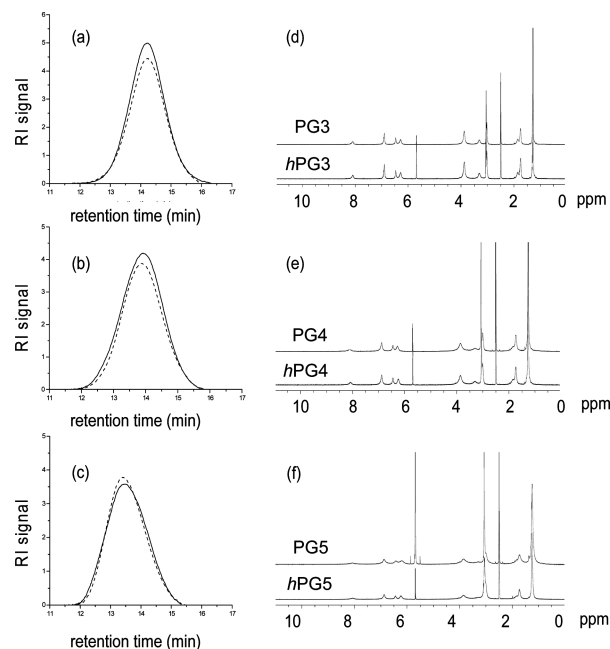

Figure 2. GPC elution curves of (a) *h***PG3** (solid) and **PG3** (dashed), (b) *h***PG4** (solid) and **PG4** (dashed), and (c) *h***PG5** (solid) and **PG5** (dashed). ¹H NMR spectra of (d) *h***PG3** and **PG3**, (e) *h***PG4** and **PG4**, and (f) *h***PG5** and **PG5** at 80 °C in DMSO-*d₆*.

samples **PG3−5**. In the ¹H NMR spectra, there is no significant difference between the products from the two approaches. Unfortunately, all the signals are too broad even at 80 °C to allow for any meaningful integration analyses, which would otherwise provide an insight into the structural integrity. From the GPC results (Figure 2 and Table 2), while *h***PG3** and **PG3** have the same retention time (14.61 min), *h***PG4** and *h***PG5** have longer retention time than their counterparts **PG4** and **PG5** by 0.17 and 0.67 min, respectively. Supposing the chain

Table 2. GPC Results of _h_PG3-5 and PG3-5

	retention time (min)	M_n (×10⁶)	PDI
_h_PG3	14.22	1.08	2.3
PG3	14.22	1.13	2.6
_h_PG4	13.92	2.40	2.7
PG4	13.90	2.37	2.6
_h_PG5	13.47	4.51	2.7
PG5	13.40	5.38	2.6

lengths for all the samples are more or less constant, these deviations should reflect the lower average molecular weight of repeat units and therefore lower structure perfections. It is also noted that the deviation of _h_PG5 in retention time is significantly larger than that of _h_PG4, which suggests even lower structural integrity. This view is confirmed by the quantitative UV measurements, by which dendron coverages for the last dendronization step using **DG2** were determined to be lower (Table 1). Different from the reference samples **PG3−5**, which have constantly >99% coverage, _h_PG3−5 clearly showed a trend for decreasing coverages upon increasing generation. While _h_PG3 has a near-quantitative coverage, _h_PG4 has a slight decrease (by ∼1%). _h_PG5 only has a coverage of 93.5%, which is significantly lower than that of the reference sample **PG5** (>99%). It should be noted that although the UV-amplification method was commonly used in the "_n_ + 1" synthesis of DP, it is still an open question whether this method is as reliable for the "_n_ + 2" approach. If the defects are buried deeper in the dendritic architectures, it may be more difficult for the external reagent (i.e., Sanger reagent) to approach. As a consequence, it cannot be excluded that the tabulated coverage values are overestimated.

Another more intuitive comparison of the DP by the two approaches comes from AFM analyses. _h_PG3−5 were adsorbed on mica and directly imaged by tapping mode AFM (Figure 3a−c). The apparent heights of _h_PG3−5 are 2.5 ± 0.5, 4.1 ± 0.5, and 6.2 ± 0.4 nm, respectively, as measured from images a−c. These values are similar to the values obtained from the reference **PG3−5** (2.4 ± 0.7, 4.0 ± 0.2, and 6.1 ± 0.4 nm, respectively).[25,29] Furthermore, each generation of _h_PG3−5 was individually coimaged with the corresponding reference samples **PG3−5** (images not shown). The DP chains observed in these images are homogeneous in appearance and height, which confirms the similarity between the DP obtained using different approaches.

3. SUMMARY AND OUTLOOK

The "_n_ + 2" approach, which is considered a hybrid between the more "precise" graft-from approach and the more "efficient" graft-to approach, was investigated to synthesize DP of high generations. Compared with the conventional graft-from ("_n_ + 1") approach, this hybrid approach produces DP in higher yields. The dendron coverages are slightly lower as the generation increases, but this can be compensated by the condensation of two postpolymerization reactions, which normally cost ∼3−5 weeks. So far we have only used the G2 dendron in the last step for the synthesis of each generation; however, if G2 dendron is used throughout the entire synthesis, this would further facilitate the production of DP with respect to the time. For instance, if **PG5** is synthesized by attaching **DG2** twice from a _de_**PG1** core, we would shorten the synthesis by four steps, which should reduce the total time by ∼2 months. This will be very beneficial to the DP synthesis. Another possible extension of this approach is regarding the use of G3 dendron, although the increasing size of the attached dendrons may lead to difficulty in retaining a near-quantitative coverage for the dendronizations.

4. EXPERIMENTAL PART

4.1. Synthesis of PG1−5. **PG1** was synthesized by RAFT polymerization of G1 monomer (MG1). The number-average degree of polymerization (P_n) is ∼500, as determined by GPC using universal calibration. **PG2−5** were synthesized by the conventional "_n_ + 1" (so-called attach-to, graft-from, or divergent) method.[25] For synthetic details see Supporting Information. The structure perfections of all the DP synthesized by the "_n_ + 1" approach are >99%, as quantified by the well-established UV labeling method.[22]

4.2. Synthesis of _h_PG3−5 by the "_n_ + 2" Approach. The second-generation dendron active ester **DG2** was synthesized according to the published procedure.[13c] _h_PG3−5 were synthesized by attaching **DG2** onto the polymer cores _de_**PG1−3**. Large excesses of **DG2** (3 equiv of **DG2** per amino group) and long reactions times (∼15−16 days) were used to guarantee the efficiency of the dendronization. The yield is typically in the range of 65−73%, and the coverage for the dendronization steps was quantified by the conventional UV-amplification method as 93.5−99.7%.

_h_**PG3**. To a solution of _de_**PG1** (55 mg, 0.1 mmol), triethylamine (40 mg, 0.4 mmol), and DMAP (7 mg, cat.) in DMF (2 mL) at 0 °C was added **DG2** (0.76 g, 0.6 mmol). The reaction mixture was warmed to rt and stirred for 15 days. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (SiO₂, CH₂Cl₂). The crude product was lyophilized from 1,4-dioxane to yield _h_**PG3** as a white powder (0.19 g, 73%). ¹H NMR (500 MHz, 353 K, DMSO-_d₆_): 1.28 (br, 72 H, ᵗBu), 1.75 (br, 17 H, OCH₂C_H₂_CH₂NH), 1.86 (br, 9 H, OC_H₂_CH₂CH₂NH), 3.02 (br, 14 H, NHC_H₂_), 3.31 (br, 10 H, NHC_H₂_), 3.88 (br, 24 H, OC_H₂_), 6.28 (br, 8 H, BocNH and Ph), 6.47 (br, 6 H, Ph), 6.90 (br, 11 H, Ph),
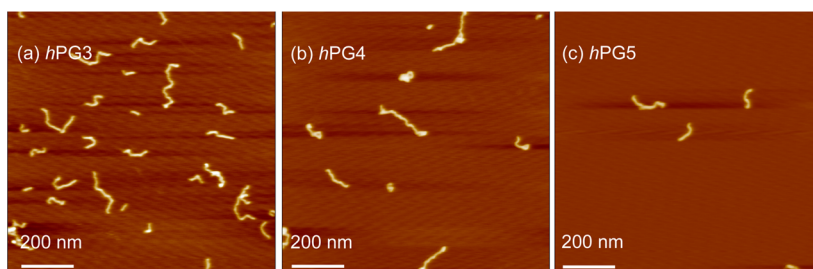

Figure 3. AFM height images on mica of (a) _h_PG3, (b) _h_PG4, and (c) _h_PG5. _h_PG3−5 were dissolved in DCM at 1−10 mg/L concentration, drop-cast on mica, and air-dried for 12 h before AFM imaging. The height scale of these images is not normalized in order to obtain good contrast; therefore, the color in each image cannot be directly compared.

8.09 (br, 5 H, CH$_2$NH). Elemental analysis (%) calcd for (C$_{135}$H$_{198}$N$_{14}$O$_{38}$)$_n$ (2625.12)$_n$: C 61.77, H 7.60, N 7.47; found: C 61.40, H 7.58, N 7.03.

*h***PG4**. To a solution of *de***PG2** (64 mg, 0.05 mmol), triethylamine (40 mg, 0.4 mmol), and DMAP (7 mg, cat.) in DMF (2 mL) at 0 °C was added **DG2** (0.76 g, 0.6 mmol). The reaction mixture was warmed to rt and stirred for 16 days. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (SiO$_2$, CH$_2$Cl$_2$). The crude product was lyophilized from 1,4-dioxane to yield *h***PG4** as a white powder (0.18 g, 68%). ^{1}H NMR (500 MHz, 353 K, DMSO-d_6): 1.26 (br, 144 H, ^{t}Bu), 1.73 (br, 32 H, OCH$_2$CH_2CH$_2$NH), 1.85 (br, 14 H, OCH$_2$CH_2CH$_2$NH), 3.01 (br, 28 H, NHCH_2), 3.30 (br, 16 H, NHCH_2), 3.86 (br, 41 H, OCH$_2$), 6.24 (br, 14 H, BocNH), 6.45 (br, 13 H, Ph), 6.88 (br, 22 H, Ph), 8.07 (br, 8 H, CH$_2$NH). Elemental analysis (%) calcd for (C$_{279}$H$_{406}$N$_{30}$O$_{78}$)$_n$ (5428.43)$_n$: C 61.73, H 7.54, N 7.74; found: C 61.66, H 7.59, N 7.44.

*h***PG5**. To a solution of *de***PG3** (82 mg, 0.03 mmol), triethylamine (48 mg, 0.48 mmol), and DMAP (4 mg, cat.) in DMF (3 mL) at 0 °C was added **DG2** (0.91 g, 0.72 mmol). The reaction mixture was warmed to rt and stirred for 16 days. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (SiO$_2$, CH$_2$Cl$_2$). The crude product was lyophilized from 1,4-dioxane to yield *h***PG4** as a white powder (0.22 g, 65%). ^{1}H NMR (500 MHz, 353 K, DMSO-d_6): 1.25 (br, 288 H, ^{t}Bu), 1.73 (br, 69 H, OCH$_2$CH_2CH$_2$NH), 1.84 (br, 27 H, OCH$_2$CH_2CH$_2$NH), 3.01 (br, 54 H, NHCH_2), 3.28 (br, 26 H, NHCH_2), 3.86 (br, 79 H, OCH$_2$), 6.23 (br, 28 H, BocNH), 6.44 (br, 24 H, Ph), 6.87 (br, 40 H, Ph), 8.07 (br, 10 H, CH$_2$NH). Elemental analysis (%) calcd for (C$_{567}$H$_{822}$N$_{62}$O$_{158}$)$_n$ (11035.05)$_n$: C 61.71, H 7.51, N 7.87; found: C 61.44, H 7.46, N 7.81.

4.3. Measurements. ^{1}H NMR measurements were performed on Bruker AV 300 (300 MHz) and 500 (500 MHz) spectrometers at room temperature. Chemical shifts are reported as δ values (ppm). Gel permeation chromatography (GPC) measurements were carried out using a PL-GPC 220 instrument with a 2 × PL-Gel Mix-B LS column set (2 × 30 cm) equipped with refractive index (RI), viscometry and light scattering (LS; 15° angle) detectors, and LiBr (1 g/L) in DMF as eluent at 45 °C. Universal calibration was performed with poly(methyl methacrylate) standards in the range of M_p = 2680−1 500 000 (Polymer Laboratories Ltd., UK). AFM measurements were performed with a Nanoscope IIIa multimode scanning probe microscope (Digital Instruments, San Diego, CA) in the tapping mode with an E scanner (scan range 10 μm × 10 μm) at ambient conditions. Olympus silicon OMCL-AC160TS cantilevers (Atomic Force F&E GmbH, Mannheim, Germany) with a resonance frequency in the 200 and 400 kHz range (typically ∼300 kHz) and a spring constant ∼42 N/m were used. The specimens for AFM measurements were prepared by drop-casting the polymer solution (3 to 4 mg/L in dichloromethane, chloroform, or methanol) onto freshly cleaved mica (PLANO W. Plannet GmbH, Wetzlar, Germany). Typical measurements were performed with amplitude set point ranging from 0.5 to 2.0 V and drive amplitude ranging from 5 to 90 mV. No deconvolution was performed. Elemental analyses were performed by the Mikrolabor of the Laboratorium für Organische Chemie, ETH Zürich.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Syntheses of **PG1**−**5** and a short chain analogue **PG1$_{40}$** (P_n ∼ 40); UV−vis spectra of *h***PG3**−**5**; end-group analysis of **PG1$_{40}$** by ^{1}H NMR spectroscopy. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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