# L-Lysine Dendronized Polystyrene

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ABSTRACT: This paper reports the synthesis and characterization of a novel class of dendronized polymers which are based on styrene functionalized dendritic L-lysine macromonomers. Free radical polymerization of zeroth and first generation macromonomers afforded dendronized polymers with number-average degrees of polymerization (DP) between 50 and 240, corresponding to number-average molecular weights between  $50 \times 10^3$  and  $240 \times 10^3$  g/mol. In contrast, only short oligomers (DP = 5–15) were obtained on polymerization of the second generation dendritic L-lysine macromonomers. Molecularly resolved AFM images allowed first insight into the structure of these peptide dendronized polymers. Depending on the degree of polymerization, either rods, short rods, or globular structures were found.

# Introduction

Dendronized polymers are polymers that contain dendritic fragments attached to a polymer backbone.<sup>1</sup> One of the most intriguing features of these macromolecules is that their overall structure can be controlled by the degree of polymerization of the backbone and the size and shape of the dendritic substituents. Percec et al. found that dendronized polymers based on styrene or methacrylate functionalized conical dendrons form spherical objects with a random coil backbone conformation at low degrees of polymerization. Increasing the degree of polymerization, however, was found to result in the formation of a cylindrical-shaped polymer with a relatively extended backbone conformation.<sup>2</sup> Because of the size of the dendritic substituents, such cylindrical polymers may have diameters of several nanometers. Furthermore, the dendritic groups generate a densely packed surface, which can suppress interlocking of individual dendronized macromolecules. As a result, appropriately designed dendronized polymers can be regarded as individual molecular objects, which could be interesting building blocks to construct larger architectures.

The chemical structure of the dendritic substituents that have been appended to polymer backbones varies widely, from Fréchet-type benzyl ether dendrons<sup>3</sup> to phenylacetylene-based structures.<sup>4</sup> A class of dendrons, however, which has only received very little attention are dendrons based on amino acids. An exception is the work by Ritter and Niggemann, who reported the synthesis and polymerization of methacrylate functionalized L-aspartic acid dendrons.<sup>5,6</sup> These authors, however, could not obtain molecular weight data of their products<sup>5</sup> and only found evidence for the formation of low molecular weight oligomers.<sup>6</sup> In a more recent series of articles, the synthesis and properties of various polyacrylates substituted with L-aspartic acid and Lglutamic acid dendrons were described.<sup>7</sup> This contribution reports the synthesis and characterization of a novel class of peptide-based dendronized polymers, which were obtained by polymerization of styrene functionalized L-lysine dendrons. Dendrimers and linear dendritic block copolymers based on L-lysine have attracted interest, e.g., for the development of multiple antigen peptides<sup>8</sup> or as vectors for gene delivery.<sup>9</sup> The L-lysine dendronized polystyrenes that will be discussed in this contribution add to these existing classes of branched L-lysine-based polymer architectures and may possess interesting properties for similar applications.

#### **Experimental Section**

**Abbreviations.** DIPEA, *N*,*N*-diisopropylethylamine; DMF, *N*,*N*-dimethylformamide; FD, field desorption; Fmoc, 9-fluorenylmethoxycarbonyl; HBTU, *O*-benzotriazole-*N*,*N*,*N'*,*N'*-tetramethyluronium hexafluorophosphate; HOBt, *N*-hydroxybenzotriazole; MALDI–TOF, matrix-assisted laser desorption– ionization time-of-flight; MS, mass spectrometry; NMP, *N*-methyl-2-pyrrolidone; SPPS, solid-phase peptide synthesis; TFA, trifluoroacetic acid or trifluoroacetamide; VBA, 4-vinylbenzylamine; Z, benzyloxycarbonyl.

**Materials.**  $N^{\alpha}$ ,  $N^{\epsilon}$ -di-TFA-L-lysine (9)<sup>10</sup> and 4-vinylbenzylamine (1)<sup>11</sup> were prepared according to literature procedures. NMP and DMF were dried over molecular sieves (4 Å). All other solvents and chemicals were purchased from commercial suppliers and used as received.

Analytical Methods. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on Bruker AMX300, DRX 500, and DPX700 spectrometers. The residual proton or carbon signal of the deuterated solvent was used as internal standard. Chemical shifts are reported in parts per million (ppm), and peak multiplicities are described using the following abbreviations: bs, broad singlet; m: multiplet; s: singlet; d: doublet; t: triplet; q: quartet; qC: quaternary carbon. Mass spectra were recorded on a VG ZAB 2-SE-FPD instrument (field desorption, FD) or a Bruker Reflex II MALDI-TOF mass spectrometer. Dithranol was used as the matrix, and samples were prepared either with DMSO as the solvent or without solvent following the solid-state procedure. In some cases, sodium trifluoracetate was added to facilitate ionization. Gel permeation chromatography (GPC) was performed on a Waters 150CV modified for on-line differential viscometry. All analyses were carried out at 60 °C using two TSK-Gel Alpha columns (3000 + 4000) in series and DMF + 1 g/L LiBr as the eluent. Elution times were

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converted into absolute molecular weights using the "universal calibration" curve, which was constructed using anionically prepared poly(methyl methacrylate) standards, in combination with the information obtained from the refractive index and differential viscometer detectors. Intrinsic viscosities were obtained in similar fashion by combination of the signals from the two detectors. Tapping mode AFM images were collected using a multimode atomic force microscope (Veeco Metrology Group) equipped with a Nanoscope IIIa controller. NSC-14 Si cantilevers (Mikromash USA) with a resonance frequency of about 160 kHz and a spring constant of about 5 N/m were used. The radius of the probe was less than 10 nm. High-resolution images of single molecules were obtained using DP-14 Hi'Res probes possessing ultra-sharp whiskers with a radius below 3.5 nm.

Procedures. Preparation of the Zeroth Generation  $N^{\alpha}$ , $N^{\epsilon}$ -Diprotected *tert*-Butyl Ester Dendrons. General procedure: the appropriate  $N^{\alpha}$ , $N^{\epsilon}$ -diprotected L-lysine derivative was dissolved in dry DMF (~0.2 M) together with 2 equiv of HBTU, 2 equiv of HOBt, and 3 equiv of DIPEA. After 5–10 min, 1.5 equiv of  $\beta$ -alanine-*tert*-butyl ester hydrochloride was added, and the reaction mixture was stirred at room temperature. After 16 h, the reaction was quenched by adding the reaction mixture to a 20-fold excess of water. The precipitate was filtered, washed extensively with water, and vacuum dried.

**Zeroth-Generation**  $N^{\alpha}$ ,  $N^{\epsilon}$ -**Di-Z-Protected** *tert*-**Butyl Ester Dendron.** Yield: 98% of a white solid. <sup>1</sup>H NMR (300 MHz, DMSO, rt):  $\delta$  (ppm) = 1.17–1.59 (m, 15H, 'Bu +  $\alpha$ CH–(CH<sub>2</sub>)<sub>3</sub>); 2.34 (t, 2H, 'BuOCO–CH<sub>2</sub>); 2.95 (q, 2H,  $\alpha$ CH(CH<sub>2</sub>)<sub>3</sub>–CH<sub>2</sub>); 3.21 (m, 2H, 'BuOCCH<sub>2</sub>–CH<sub>2</sub>); 3.89 (q, 1H,  $\alpha$ CH); 4.99 (s, 2H, Z CH<sub>2</sub>); 7.24 (t, 1H, NH); 7.33 (m, 11H, arom CH +  $\alpha$ CH–NH); 7.94 (t, 1H, NH). <sup>13</sup>C NMR (75 MHz, DMSO, 298 K):  $\delta$  (ppm) = 23.23 (CH<sub>2</sub>); 28.20 (CH<sub>2</sub>); 29.56 (CH<sub>2</sub>); 32.13 (CH<sub>2</sub>); 35.30 (CH<sub>2</sub>); 55.13 ( $\alpha$ CH); 65.58 (CH<sub>2</sub>); 65 83 (arom CH); 80.35 (qC); 128.19 ( $N^{\epsilon}$ -Z arom CH); 128.81 ( $N^{\alpha}$ -Z arom CH); 137.5, 137.76 (Z arom qC); 156.39 (CO); 156.54 (CO); 171.05 ( $\alpha$ CH–CO); 172.39 (CO). MS (FD): m/z = 543 (100% [M]<sup>+</sup>); 1085 (15% [2M]<sup>+</sup>).

Zeroth Generation  $N^{\alpha}$ ,  $N^{\epsilon}$ -Di-TFA-Protected *tert*-Butyl Ester Dendron. Yield: 98% of a white solid. <sup>1</sup>H NMR (300 MHz, DMSO, rt):  $\delta$  (ppm) = 1.23 (m, 2H,  $\alpha$ CHCH<sub>2</sub>-CH<sub>2</sub>); 1.39 (m, 11H,  ${}^{t}Bu + \alpha CH - CH_{2}$ ); 1.66 (q, 2H,  $\alpha CH(CH_{2})_{2} - CH_{2}$ ); 2.35  $(t, 2H, {}^{t}BuOCO-CH_{2}); 3.14 (m, 2H, \alpha CH(CH_{2})_{3}-CH_{2}); 3.25 (m,$ 2H, <sup>t</sup>BuOOCCH<sub>2</sub>-CH<sub>2</sub>); 4.22 (t, 1H, αCH); 8.19 (t, 1H, NH); 9.4 (t, 1H, NH); 9.5 (d, 1H, αCH-NH). <sup>13</sup>C NMR (75 MHz, DMSO, 298 K):  $\delta$  (ppm) = 23.63, 23.76 (CH<sub>2</sub>); 28.59 (CH<sub>2</sub>); 28.63 (CH<sub>3</sub>); 30.34 (CH<sub>2</sub>); 31.67 (CH<sub>2</sub>) 35.74, 35.89 (CH<sub>2</sub>); 39.71(CH<sub>2</sub>); 53.42, 54.18 (aCH); 80.84 (qC); 111.06, 114.88, 118.69, 122.51  $(N^{\alpha}-CF_3)$ ; 111.19, 115.00, 118.82, 122.64  $(N^{\epsilon}-CF_3)$ ; 156.78, 156.82, 157.01, 157.26, 157.35, 157.50, 157.75, 157.82 (CO–CF<sub>3</sub>); 171.01, 171.43 ( $\alpha$ CH–CO); 172.87 (CO). <sup>19</sup>F NMR (282 MHz, DMSO, 298 K):  $\delta$  (ppm) = -73.91, 73.95, -74.12,  $-74.16 (N^{\alpha}-CF_3); -74.44, -74.47 (N^{\epsilon}-CF_3).$  MS (FD): m/z =466.6 (100% [M]<sup>+</sup>); 932.8 (21% [2M]<sup>+</sup>).

**Preparation of the Zeroth Generation**  $N^{\alpha}, N^{\epsilon}$ -Diprotected Carboxylic Acid Dendrons (2a,b). General procedure: ~3 g of the appropriate zeroth generation  $N^{\alpha}, N^{\epsilon}$ diprotected *tert*-butyl ester dendron was dissolved in as little as possible of a 50/50 (v/v) mixture of CH<sub>2</sub>Cl<sub>2</sub> and TFA and stirred at room temperature for 2 h. After that, solvents were removed at the rotary evaporator, and the residue was triturated with water (2a) or ice-cold diethyl ether (2b). Finally, the solids were isolated by filtration and vacuumdried.

**2a:** 2.64 g (5.5 mmol, 98%) of a white solid. <sup>1</sup>H NMR (300 MHz, DMSO, rt):  $\delta$  (ppm) = 1.14–1.67 (m, 6H,  $\alpha$ CH–(CH<sub>2</sub>)<sub>3</sub>); 2.38 (t, 2H, HOCO–CH<sub>2</sub>); 2.96 (q, 2H,  $\alpha$ CH(CH<sub>2</sub>)<sub>3</sub>–CH<sub>2</sub>–); 3.23 (m, 2H, HOOCCH<sub>2</sub>–CH<sub>2</sub>); 3.90 (m, 1H,  $\alpha$ CH); 5.01 (m, 4H, Z CH<sub>2</sub>); 7.26 (t, 1NH,  $\alpha$ CH–NH); 7.36 (m, 11H, arom CH +  $\alpha$ CH–NH); 7.96 (t, 1NH,  $\alpha$ CHCO–NH). <sup>13</sup>C NMR (75 MHz, DMSO, 298 K):  $\delta$  (ppm) = 23.7 (CH<sub>2</sub>); 30.01 (CH<sub>2</sub>); 32.59 (CH<sub>2</sub>); 34.90 (CH<sub>2</sub>); 35.74, 35.85 (CH<sub>2</sub>); 40.91 (CH<sub>2</sub>) 55.49 ( $\alpha$ CH); 66.05, 66.31 (CH<sub>2</sub>); 128.67 (N<sup> $\alpha$ </sup>–Z arom CH); 129.28 (N<sup> $\alpha$ </sup>–Z arom qC); 137.99, 138.22 (Z arom qC); 156.87, 156.87 (NH–

 $\begin{array}{l} {\rm CO-O);\ 172.82\ (\alpha CH-CO);\ 173.96\ (COOH).\ MS\ (FD):\ m/z = } \\ {\rm 486.1\ (100\%\ [M]^+);\ 508.1\ (92\%\ [M-Na]^+);\ 524\ (12\%\ [M-K]^+);} \\ {\rm 993.2\ (80\%\ [2M]^+);\ 1477.9\ (7\%\ [3M]^+).} \end{array}$ 

**2b:** Yield: 2.59 (6,2 mmol, 99%) of a white solid. <sup>1</sup>H NMR (250 MHz, DMSO, 298 K):  $\delta$  (ppm) = 1.25 (m, 2H,  $\alpha$ CHCH<sub>2</sub>- $CH_2$ ; 1.44 (m, 2H,  $\alpha CH - CH_2$ ); 1.67 (q, 2H,  $\alpha CH(CH_2)_2 - CH_2$ ); 2.38 (t, 2H, HOCO-CH<sub>2</sub>); 3.20 (m, 2H, αCH(CH<sub>2</sub>)<sub>3</sub>-CH<sub>2</sub>); 3.28 (m, 2H, HOOCCH<sub>2</sub>–CH<sub>2</sub>); 4.23 (q, 1H,  $\alpha$ CH); 8.20 (t, 1H, N<sup> $\epsilon$ </sup>-NH); 9.40 (t, 1H, αCHCO-NH); 9.49 (d, 1H, αCH-NH); 12.72 (bs, 1H, COOH).  $^{13}\mathrm{C}$  NMR (75 MHz, DMSO, 298 K):  $\delta$  (ppm)  $= 23.67 (CH_2); 28.73 (CH_2); 31.66 (CH_2); 34.62 (CH_2); 35.75,$ 35.87 (CH<sub>2</sub>); 39.82, 39.94 (CH<sub>2</sub>); 54.12, 54.21 (aCH); 111.10, 114.91, 118.73, 122.55 ( $N^{\alpha}$ -CF<sub>3</sub>); 111.23, 115.04, 118.86, 122.68  $(N^{\epsilon}-CF_3)$ ; 156.43, 156.53, 156.61, 156.83, 156.91, 157.01, 157.10, 157.30, 157.38, 157.50, 157.58, 157.78, 157.86, 157.99, 158.06 (CO-CF<sub>3</sub>); 171.08 (aCH-CO); 173.72 (COOH). <sup>19</sup>F NMR (282 MHz, DMSO, 298 K):  $\delta$  (ppm) = -73.93, -73.96  $(N^{\alpha}-CF_3)$ ; -74.46, -74.49  $(N^{\epsilon}-CF_3)$ .  $\hat{MS}$  (FD): m/z = 410.3(100% [M]<sup>+</sup>); 819.6 (9% [2M]<sup>+</sup>).

First and Second Generation Dendrons. First generation dendrons were prepared on a 4-hydroxymethyl-3-methoxyphenoxybutyric (HMPB)-BHA-resin (loading: 0.61 mmol/ g). The synthesis of the second generation dendrons was performed on a Tentagel S AC-resin (loading: 0.24 mmol/g). The L-lysine dendrons were prepared using standard Fmoc SPPS protocols.<sup>12</sup> Peptide bond formation was facilitated by the use of HBTU/HOBt. The first two amino acids were coupled to the resin using an automated peptide synthesizer (Applied Biosystems ABI 433A). After that, the resin was taken from the synthesizer, and the preparation of the first and second generation dendrons was completed manually. In the case of the first generation dendrons, the resin-bound dipeptide swollen in NMP was treated with 2.5 equiv of the appropriate amino acid derivative, 5 equiv of HBTU/HOBt, and 7 equiv of DIPEA and gently shaken for 16 h at room temperature. In the last coupling step for the preparation of the second generation dendrons, 1 equiv of resin-bound amine groups was treated with 4 equiv of the appropriate amino acid, 8 equiv of HBTU/HOBt, and 12 equiv of DIPEA and gently shaken for 9 h at room temperature. The dendrons were cleaved from the support by treating the resin-bound product three times for a period of 30 min with a 3% (v/v) of TFA in CH<sub>2</sub>Cl<sub>2</sub>. Subsequently, the combined washings were evaporated under vacuum, and the residual solid was triturated with water to afford a fine powder, which was filtered and vacuumdried. Dendron **3b**, after evaporation of TFA/CH<sub>2</sub>Cl<sub>2</sub>, however, was dissolved in acetone and precipitated in a 20-fold excess of *n*-hexane.

**3a:** Yield: 79% of a beige solid. <sup>1</sup>H NMR (300 MHz, DMSO, 298 K):  $\delta$  (ppm) = 1.1–1.7 (m, 18H,  $\alpha$ CH–(CH<sub>2</sub>)<sub>3</sub>); 2.35 (t, 2H, HOOC–CH<sub>2</sub>); 2.95 (m, 6H,  $\alpha$ CH(CH<sub>2</sub>)<sub>3</sub>–CH<sub>2</sub>); 3.89, 3.97 (m, 2H, outer  $\alpha$ CH); 4.15 (m, 1H, inner  $\alpha$ CH); 5.01 (m, 8H, Z CH<sub>2</sub>) 7.23 (t, NH); 7.34 (m, 20H, arom CH); 7.85 (d, NH); 7.95 (t, NH). <sup>13</sup>C NMR (75 MHz, DMSO, 298 K):  $\delta$  (ppm) = 23.47, 23.73 (CH<sub>2</sub>); 29.66, 29.97 (CH<sub>2</sub>); 32.41, 32.63, 32.79 (CH<sub>2</sub>); 34.69 (CH<sub>2</sub>); 35.60, 35.72 (CH<sub>2</sub>); 39.36 (CH<sub>2</sub>); 53.20 (outer  $\alpha$ CH); 55.62 (inner  $\alpha$ CH); 66.01 (*N*<sup>e</sup>Z–CH<sub>2</sub>); 66.26, 66.30 (*N*<sup>a</sup>Z–CH<sub>2</sub>) 128.57, 128.61 (*N*<sup>e</sup>Z arom CH); 129.23 (*N*<sup>a</sup>Z arom CH); 137.92, 137.96, 138.19 (arom qC); 156.78, 156.83, 156.91, 156.97 (Z-CO); 172.27, 172.35, 172.55, 172.62 (CO); 173.69 (COOH). MS (MALDI–TOF, dithranol, DMSO): *m/z* = 1032 (50% [M + Na]<sup>+</sup>); 1048 (39% [M + K]<sup>+</sup>).

**3b:** Yield: 91% of a beige solid. <sup>1</sup>H NMR (300 MHz, DMSO, 298 K):  $\delta$  (ppm) = 1.24 (bs, 6H,  $\alpha$ CHCH<sub>2</sub>-CH<sub>2</sub>); 1.47 (bs, 6H,  $\alpha$ CH-CH<sub>2</sub>), 1.69 (m, 6H,  $\alpha$ CH(CH<sub>2</sub>)<sub>2</sub>-CH<sub>2</sub>); 2.37 (m, 2H, HOOC-CH<sub>2</sub>); 3.01, 3.15 (s, 2H,  $\alpha$ CH(CH<sub>2</sub>)<sub>3</sub>-CH<sub>2</sub>); 3.24 (m, 2H, HOOCCH<sub>2</sub>-CH<sub>2</sub>); 4.20 (m, 2H, outer  $\alpha$ CH); 4.35 (m, 1H, inner  $\alpha$ CH); 7.98 (t, NH); 8.07 (t, NH); 8.12 (d, NH); 8.29 (d, NH); 9.38 (t, NH); 9.47 (m, 2NH); 12.21 (bs, 1H, COOH). <sup>13</sup>C NMR (75 MHz, DMSO, 298 K):  $\delta$  (ppm) = 23.65 (CH<sub>2</sub>); 28.68, 29.50, 29.60, 31.51, 31.67, 31.75, 32.72, 32.78, 34.60, 35.75, 39.40, 39.50 (CH<sub>2</sub>); 53.20, 53.50 (outer  $\alpha$ CH); 54.24 (inner  $\alpha$ CH); 111.06, 114.87, 118.69, 122.51 ( $N^{\alpha}$ -CF<sub>3</sub>) 111.18, 115.00, 118.82, 122.64 ( $N^{\epsilon}$ -CF<sub>3</sub>); 156.38, 156.86, 157.33, 157.81 ( $N^{\alpha}$ -CF<sub>3</sub>-CO); 156.56, 157.04, 157.53, 158.01 ( $N^{\epsilon}$ -CF<sub>3</sub>-CO); 170.67,

170.75, 170.86, 170.94, 172.08, 172.18, 172.28, 173.63, 173. 71 (CO + COOH). <sup>19</sup>F NMR (282 MHz, DMSO, rt):  $\delta$  (ppm) = -73.86, -73.88, 73.90 ( $N^{\alpha}$ -CF<sub>3</sub>), -74.40, -74.41 ( $N^{\epsilon}$ -CF<sub>3</sub>). MS (MALDI-TOF, solid state, Na): m/z = 841 (8% ([M<sup>+</sup> - OH]); 880 (90% [M + Na]<sup>+</sup>); 896 (14% [M + K]<sup>+</sup>); 902 (59% [M + 2Na]<sup>+</sup>); 918 (7% [M + Na + K]<sup>+</sup>); 924 (7% [M + 3Na]<sup>+</sup>).

**4a:** Yield: 65% of a beige solid. <sup>1</sup>H NMR (300 MHz, DMSO, 298 K):  $\delta$  (ppm) = 1.08–1.74 (m, 42H,  $\alpha$ CH–(CH<sub>2</sub>)<sub>3</sub>); 2.36 (t, 2H, HOOC–CH<sub>2</sub>); 2.95 (bs, 14H,  $\alpha$ CH(CH<sub>2</sub>)<sub>3</sub>–CH<sub>2</sub>); 3.24 (m, 2H, HOOCCH<sub>2</sub>–CH<sub>2</sub>); 3.93 (m, 4H, outer  $\alpha$ CH); 4.19 (m, 3H, inner  $\alpha$ CH); 5.0 (m, 16H, Z CH<sub>2</sub>); 7.33 (m, 40H, arom. CH + 7NH); 7.73–8.02 (m, 8NH); 12.13 (COOH). <sup>13</sup>C NMR (75 MHz, DMSO, 298 K):  $\delta$  (ppm) = 23.55, 23.72 (CH<sub>2</sub>); 29.67, 29.97 (CH<sub>2</sub>); 32.41, 32.63 (CH<sub>2</sub>); 34.61 (CH<sub>2</sub>); 35.67 (CH<sub>2</sub>); 39.39 (CH<sub>2</sub>); 53.26 (outer  $\alpha$ CH); 55.62 (inner  $\alpha$ CH); 66.02 (N<sup>e</sup>–Z CH<sub>2</sub>); 66.27 (N<sup> $\alpha$ </sup>–Z CH<sub>2</sub>); 128.60 (N<sup>e</sup>–Z arom); 129.22 (N<sup> $\alpha$ </sup>–Z arom); 137.89, 137.94 (N<sup> $\alpha$ </sup>–Z arom qC); 138.17 (N<sup>e</sup>–Z arom qC); 156.83, 156.91, 156.97 (Z CO); 172.09, 172.23, 172.28, 172.54, 172.62, 172.87 (CO); 173.66 (COOH). MS (MALDI–TOF, dithranol, DMSO): *m*/*z* = 2083 (46% [M + Na]<sup>+</sup>), 2099 (21% [M + K]<sup>+</sup>).

**4c:** Yield: 74% of a beige solid. <sup>1</sup>H NMR (300 MHz, DMSO, 298 K):  $\delta$  (ppm) = 0.99–1.80 (m, 42H,  $\alpha$ CH–(CH<sub>2</sub>)<sub>3</sub>); 2.95 (bs, 14H,  $\alpha$ CH(CH<sub>2</sub>)<sub>3</sub>–CH<sub>2</sub>); 3.89, 3.97 (m, 4H, outer  $\alpha$ CH); 4.14 (m, 2H, middle  $\alpha$ CH); 4.27 (m, 1H, inner  $\alpha$ CH); 4.99 (m, 16H, Z CH<sub>2</sub>); 7.21 (t, NH); 7.33 (m, 40H, arom CH); 7.83 (t, NH); 8.08 (d, NH); 12.55 (COOH). <sup>13</sup>C NMR (75 MHz, DMSO, 298 K):  $\delta$  (ppm) = 23.40, 23.54, 23.72 (CH<sub>2</sub>); 29.65, 29.96 (CH<sub>2</sub>); 32.39, 32.61, 32.77 (CH<sub>2</sub>); 39.26, 39.37, 39.45 (CH<sub>2</sub>); 52.72, 52.97, 53.23 (inner  $\alpha$ CH); 55.61 (outer  $\alpha$ CH); 66.02 (N<sup>e</sup>–Z CH<sub>2</sub>), 66.27 (N<sup> $\alpha$ </sup>–Z CH<sub>2</sub>); 128.60 (N<sup>e</sup>–Z arom CH); 129.22 (N<sup> $\alpha$ </sup>–Z arom CH); 137.90, 137.94 (N<sup> $\alpha$ </sup>–Z arom qC); 138.17 (N<sup>e</sup>–Z arom qC); 166.82, 156.86, 156.92, 156.97 (Z–CO); 172.10, 172.53, (CO); 174.31 (COOH). MS (MALDI–TOF, dithranol, DMSO): m/z = (13% [M – 1Z]<sup>+</sup>); 2012 (31% [M + Na]<sup>+</sup>); 2028 (64% [M + K]<sup>+</sup>).

 $N^{\alpha}$ ,  $N^{\epsilon}$ -Diprotected L-Lysine Dendronized Styrene Macromonomers. General procedure: the appropriate  $N^{\alpha}$ ,  $N^{\epsilon}$ diprotected L-lysine dendron was dissolved in dry NMP, together with HBTU, HOBt, and DIPEA. After 5–10 min, **1** was added, and the reaction mixture was stirred at room temperature. The relative amounts of dendron, **1**, HBTU, HOBt, and DIPEA as well as the amounts of solvent and the reactions time are listed below for each of the dendronized macromonomers. The reaction was quenched by addition of a 20-fold excess of bidistilled water. To remove excess and unreacted **1**, the pH of the aqueous phase was adjusted to pH 7, and subsequently the solid residue was excessively washed with bidistilled water. In the case of macromonomer **6**b, the solid obtained after the addition of water was dissolved in acetone and subsequently precipitated in *n*-hexane.

**5a**: Reaction conditions: **2a**:**1**:HBTU:HOBt:DIPEA = 1:2: 2:2:3; 28 mL of NMP; reaction time: 16 h. Yield: 3.61 g (6 mmol, 97%) of a white solid. <sup>1</sup>H NMR (300 MHz, DMSO, 298 K):  $\delta$  (ppm) = 1.23-1.53 (m, 6H,  $\alpha$ CH-(CH<sub>2</sub>)<sub>3</sub>); 2.32 (t, 2H, VBA-CO-CH<sub>2</sub>); 2.95 (q, 2H,  $\alpha$ CH(CH<sub>2</sub>)<sub>3</sub>-CH<sub>2</sub>); 3.27 (q, 2H, VBA-COCH<sub>2</sub>-CH<sub>2</sub>); 3.90 (m, 1H, aCH); 4.25 (d, 2H, VBA CH<sub>2</sub>); 5.00 (m, 4H, Z-CH<sub>2</sub>); 5.21 (d, 1H, CH=CH<sub>2</sub>); 5.78 (d, 1H, CH=CH<sub>2</sub>); 6.70 (dd, 1H, CH=CH<sub>2</sub>); 7.21 (d, 2H, VBA arom CH); 7.32 (m, 7H, Z arom CH + 2NH); 7.41 (d, 2H, VBA arom CH); 7.97 (t, NH); 8.38 (t, NH). <sup>13</sup>C NMR (75 MHz, DMSO, 298 K):  $\delta$  (ppm) = 23.71 (CH<sub>2</sub>); 30.01 (CH<sub>2</sub>); 32.56 (CH<sub>2</sub>); 36.10 (CH<sub>2</sub>); 36.24 (CH<sub>2</sub>); 40.44 (CH<sub>2</sub>); 42.71 (CH<sub>2</sub>); 55.61 (αCH); 66.03, 66.29 (Z-CH<sub>2</sub>); 114.72 (CH=CH<sub>2</sub>); 126.98 (VBA arom CH): 126.98 (VBA arom CH): 128.39 (N<sup>α</sup>-Z arom CH): 128.64  $(N^{\epsilon}-Z \text{ arom CH})$ ; 129.26 (VBA arom CH); 136.61 (VBA arom qC); 137.31 (CH=CH<sub>2</sub>); 137.96 ( $N^{\alpha}$ -Z arom qC); 138.19, ( $N^{\epsilon}$ -Z arom qC); 140.16 (VBA arom qC); 156.85, 157.0 (Z-CO); 171.24 (CO); 172.81 (CO). MS (FD):  $m/z = 601.8 (100\% [M]^+)$ .

**5b**: Reaction conditions: **2b**:1:HBTU:HOBt:DIPEA = 1:2: 2:2:3; 35 mL of NMP; reaction time: 16 h. Yield: 3.75 g (7.2 mmol, 98%) of a white solid. <sup>1</sup>H NMR (300 MHz, DMSO, 298 K):  $\delta$  (ppm) = 1.29 (q, 2H, αCHCH<sub>2</sub>-CH<sub>2</sub>); 1.43 (q, 2H, αCH-CH<sub>2</sub>); 1.67 (q, 2H, αCH(CH<sub>2</sub>)<sub>2</sub>-CH<sub>2</sub>); 2.33 (t, 2H, VBA-CO-CH<sub>2</sub>); 3.15 (q, 2H, αCH(CH<sub>2</sub>)<sub>3</sub>-CH<sub>2</sub>); 3.26, (m VBA-COCH<sub>2</sub>- CH<sub>2</sub>); 4.21 (s, 1H, αCH); 4.25 (d, 2H, VBA CH<sub>2</sub>); 5.22 (dd, 1H, CH=CH<sub>2</sub>); 5.79 (dd, 1H, CH=CH<sub>2</sub>); 6.71 (q, 1H, CH=CH<sub>2</sub>); 7.22 (d, 2H, VBA arom CH); 7.41 (d, 2H, VBA arom CH); 8.2 (t, NH); 8.38 (t, TFA-NH); 9.40 (t, NH); 9.47 (d, 1H, αCH-NH). <sup>13</sup>C NMR (75 MHz, DMSO, 298 K): δ (ppm) = 23.18 (CH<sub>2</sub>); 28.21 (CH<sub>2</sub>); 31.14 (CH<sub>2</sub>); 33.53 (CH<sub>2</sub>); 35.86 (CH<sub>2</sub>); 39.32 (CH<sub>2</sub>); 42.26 (CH<sub>2</sub>); 53.62 (αCH); 114.28 (CH=CH<sub>2</sub>); 126.51, 127.93 (VBA arom CH); 136.16 (CH=CH<sub>2</sub>); 136.83 (VBA arom qC); 139.69 (VBA arom qC); 170.50 (CO); 170.65 (CO). <sup>19</sup>F NMR (282 MHz, DMSO, 298 K): δ (ppm) = -73.83 (N<sup>α</sup>-CF<sub>3</sub>); -74.37 (N<sup>ε</sup>-CF<sub>3</sub>). MS (FD): m/z = 525.0 (71% [M]<sup>+</sup>); 547.1 (100% [M + Na]<sup>+</sup>), 563.1 (18% [M+ K]<sup>+</sup>).

**6a:** Reaction conditions: **3a**:**1**:HBTU:HOBt:DIPEA = 1:2: 2:2:3; 8 mL of NMP; reaction time: 16 h. Yield: 1.57 g (1.4 mmol, 94%) of a beige solid. <sup>1</sup>H NMR (300 MHz, DMSO, 298 K):  $\delta$  (ppm) = 1.07-1.73 (m, 18H,  $\alpha$ CH-(CH<sub>2</sub>)<sub>3</sub>); 2.31 (t, 2H, VBA $-CO-CH_2$ ); 2.96 (bs, 6H,  $\alpha CH(CH_2)_3-CH_2$ ); 3.27 (m, 2H, VBA-COCH<sub>2</sub>-CH<sub>2</sub>); 3.89, 3.98 (2m, 2H, outer αCH); 4.17 (m, 1H, inner αCH); 4.25 (d, 2H, VBA CH<sub>2</sub>); 5.0 (m, 8H, Z CH<sub>2</sub>); 5.21 (dd, 1H, CH=CH<sub>2</sub>); 5.78 (dd, 1H, CH=CH<sub>2</sub>); 6.7 (q, 1H, CH=CH<sub>2</sub>); 7.21 (d, 2H, VBA arom CH); 7.33 (m, 20H, Z arom CH + 3NH); 7.4 (d, 2H, VBA arom CH); 7.84 (d, 3H, NH); 7.95 (t, 1H, NH); 8.36 (t, 1H, NH). 13C NMR (75 MHz, DMSO, 298 K):  $\delta$  (ppm) = 23.49, 23.73 (CH<sub>2</sub>); 29.67, 29.98 (CH<sub>2</sub>); 32.41, 32.65, 32.81 (CH<sub>2</sub>); 36.04, 36.23 (CH<sub>2</sub>); 39.37 (CH<sub>2</sub>); 42.61, 42.72 (CH<sub>2</sub>); 49.39 (VBA CH<sub>2</sub>) 53.26 (outer αCH); 55.62 (inner  $\alpha$ CH); 66.02 (N<sup> $\epsilon$ </sup>-Z-CH<sub>2</sub>); 66.27 (N<sup> $\alpha$ </sup>-Z-CH<sub>2</sub>); 114.70 (CH=  $CH_2$ ); 126.95, 128.37 (VBA arom CH); 128.61 ( $N^{\alpha}$ -Z arom CH); 129.23 (N<sup>e</sup>-Z arom CH); 136.60 (VBA arom qC); 137.28 (CH= CH<sub>2</sub>); 137.91, 137.95 (Z arom qC); 138.17 (VBA arom qC); 156.84, 156.91, 156.98 (Z CO); 171.07, 171.15, 172.22, 172.30, 172.55, 172.64 (CO). MS (MALDI-TOF, dithranol, DMSO):  $m/z = 1148 \ (100\% \ [M + Na]^+).$ 

**6b:** Reaction conditions: **3b**:**1**:HBTU:HOBt:DIPEA = 1:6: 3:3:4.5; 12 mL of NMP; reaction time: 8 h. Yield: 1.45 g (1.5 mmol, 85%) of a white solid. <sup>1</sup>H NMR (300 MHz, DMSO, 298 K):  $\delta$  (ppm) = 1.24 (q, 2H,  $\alpha$ CHCH<sub>2</sub>-CH<sub>2</sub>); 1.47 (q, 2H,  $\alpha$ CH-CH<sub>2</sub>); 1.69 (q, 2H, αCH(CH<sub>2</sub>)<sub>2</sub>-CH<sub>2</sub>); 2.32 (t, 2H, VBA-CO-CH<sub>2</sub>); 3.15 (q, 2H, αCH(CH<sub>2</sub>)<sub>3</sub>-CH<sub>2</sub>); 3.3 (2H, VBA-CO-CH<sub>2</sub>CH<sub>2</sub>); 4.18 (m, 2H, outer αCH); 4.25 (d, 2H, VBA CH<sub>2</sub>); 4.35 (m, 1H, inner αCH); 5.21 (dd, 1H, CH=CH<sub>2</sub>); 5.79 (dd, 1H, CH=CH<sub>2</sub>); 6.70 (q, 1H, CH=CH<sub>2</sub>); 7.21 (d, 2H, VBA-CH); 7.41 (d, 2H, VBA arom CH); 8.29 (t, NH); 8.38 (t, TFA-NH); 9.38 (t, NH); 9.47 (d, 1H, aCH-NH). <sup>13</sup>C NMR (75 MHz, DMSO, 298 K):  $\delta$  (ppm) = 23.73 (CH<sub>2</sub>); 28.68 (CH<sub>2</sub>); 31.47, 31.64, 31.78 (CH<sub>2</sub>); 36.06 (CH<sub>2</sub>); 36.08 (CH<sub>2</sub>); 39.48 (CH<sub>2</sub>); 42.71 (CH<sub>2</sub>); 53.19 (inner αCH); 54.20 (outer αCH); 111.03, 114.84, 118.66, 122.48 ( $N^{\alpha}$ -CF<sub>3</sub>); 111.14, 114.96, 118.78, 122.60 ( $N^{\epsilon}$  $CF_3$ ) 114.69 (CH= $CH_2$ ); 126.95, 128.37 (VBA arom CH); 136.60 (VBA arom qC); 137.28 (CH=CH<sub>2</sub>); 140.12 (VBA arom qC);  $156.33, 156.81, 157.28, 157.76 (N^{\alpha} - CF_3 - CO); 156.51, 157.00,$ 157.48, 157.97 ( $N^{\epsilon}$ -CF<sub>3</sub>-CO) 170.71, 170.87, 170.91, 171.06, 171.17 (CO); 172.10, 172.16 (CO). <sup>19</sup>F NMR (282 MHz, DMSO, rt):  $\delta$  (ppm) = -73.86, -73.88, 73.89 ( $N^{\alpha}$ -CF<sub>3</sub>), -74.40, -74.41 ( $N^{\epsilon}$ -CF<sub>3</sub>). MS (FD): m/z = 995 (100% [M + Na]<sup>+</sup>), 1017  $(6\% [M + 2Na]^+).$ 

**7a:** Reaction conditions: **4a**:**1**:HBTU:HOBt:DIPEA = 1:3: 3:2.5:4; 15 mL of NMP; reaction time: 16 h. Yield: 1.81 g (0.83 mmol, 95%) of a beige solid. <sup>1</sup>H NMR (300 MHz, DMSO, 298 K):  $\delta$  (ppm) = 1.06–1.73 (m, 42H,  $\alpha$ CH–(CH<sub>2</sub>)<sub>3</sub>); 2.31 (t, 2H, VBA $-CO-CH_2$ ; 2.96 (bs, 14H,  $\alpha CH(CH_2)_3-CH_2$ ); 3.3 (m, 2H, VBA-COCH<sub>2</sub>-CH<sub>2</sub>); 3.89, 3.97 (2m, 4H, outer αCH); 4.16 (m, 3H; inner αCH); 4.25 (bs, 2H, VBA CH<sub>2</sub>); 5.0 (m, 16H, Z CH<sub>2</sub>); 5.21 (d, 1H, CH=CH<sub>2</sub>); 5.78 (d, 1H, CH=CH<sub>2</sub>); 6.69 (q, 1H, CH-CH<sub>2</sub>); 7.2 (d, 2H, VBA arom CH); 7.33 (m, 40H, Z arom CH + 7NH); 7.39 (d, 2H, VBA arom CH); 7.84 (bs, 7NH); 7.93 (bs, 1NH); 8.36 (t, 1NH). <sup>13</sup>C NMR (75 MHz, DMSO, 298 K):  $\delta$  (ppm) = 23.58, 23.73 (CH<sub>2</sub>); 29.67, 29.97 (CH<sub>2</sub>); 32.14, 31.60, 32.82 (CH<sub>2</sub>); 36.05, 36.25 (CH<sub>2</sub>); 39.39 (CH<sub>2</sub>); 42.63, 42.71 (CH<sub>2</sub>); 49.40 (VBA CH<sub>2</sub>); 53.26 (outer αCH); 55.61 (inner αCH), 66.02 ( $N^{\epsilon}$ -Z-CH<sub>2</sub>); 66.27 ( $N^{\alpha}$ -Z-CH<sub>2</sub>); 114.72 (CH=CH<sub>2</sub>); 126.98 (VBA arom CH); 128.36 (VBA arom CH); 128.60 ( $N^{\alpha}$ –Z arom CH); 129.23 (Ne-Z arom CH); 136.58, 137.88, 137.94 (Z arom qC); 137.27 (CH=CH<sub>2</sub>); 138.17 (VBA arom qC) 140.11 (VBA arom qC); 156.83, 156.92, 156.98 (Z CO); 171.08, 171.16, Scheme 1



172.14, 172.22, 172.56 (CO). MS (MALDI–TOF, dithranol, DMSO):  $m/z = 2198 \ (100\% \ [M + Na]^+).$ 

7c: Yield: 1.28 g (0.61 mmol, 93%) of a beige solid. <sup>1</sup>H NMR (300 MHz, DMSO, 298 K):  $\delta$  (ppm) = 1.02–1.81 (m, 42H, αCH-(CH<sub>2</sub>)<sub>3</sub>); 2.96 (bs, 14H, αCH(CH<sub>2</sub>)<sub>3</sub>-CH<sub>2</sub>); 3.89-4.06 (2m, 4H, outer  $\alpha$ CH); 4.1–4.38 (m, 5H; inner  $\alpha$ CH + VBA CH<sub>2</sub>); 5.0 (m, 16H, Z C 2); 5.19 (dd, 1H, CH=CH2); 5.77 (dd, 1H, CH= CH<sub>2</sub>); 6.6-6.76 (m, 1H, CH-CH<sub>2</sub>); 6.82-7.52 (m, arom CH); 7.71, 8.00, 8.20, 8.37 (NH). <sup>13</sup>C NMR (75 MHz, DMSO, 298 K):  $\delta$  (ppm) = 23.55, 23.72 (CH<sub>2</sub>); 29.67, 29.97 (CH<sub>2</sub>); 32.39, 32.64, 32.82 (CH<sub>2</sub>); 39.37 (CH<sub>2</sub>); 42.72 (VBA CH<sub>2</sub>) 53.25, 53.53 (inner  $\alpha$ CH); 55.61 (outer  $\alpha$ CH), 66.02 ( $N^{\epsilon}$ -Z-CH<sub>2</sub>), 66.27  $(N^{\alpha}-Z-CH_2)$ ; 114.70 (CH=CH<sub>2</sub>); 126.90 (VBA arom CH); 128.22 (VBA arom CH); 128.60 ( $N^{\alpha}$ -Z arom CH); 129.22 ( $N^{\epsilon}$ -Z arom CH); 136.53, 136.59 (Z arom qC); 137.25 (CH=CH<sub>2</sub>); 137.89 (VBA arom qC) 137.94 (VBA arom qC); 156.82, 156.97 (Z-CO); 172.09, 172.35, 172.54, 172.61, 173.21 (CO). MS (MALDI-TOF, dithranol, DMSO): m/z = 2128 (100% [M + Na]+).

**Polymerization Experiments.** Polymerizations were performed in Schlenk tubes, which were charged with the appropriate amounts of macromonomer, solvent, and initiator (AIBN, 1 mol %). After three "freeze-pump-thaw" cycles, the Schlenk tube was heated to 70 °C under an argon atmosphere, and the polymerization was allowed to proceed for 3 days. After that, the polymers were precipitated in water (Z-protected dendronized polystyrenes) or diethyl ether (TFA-protected dendronized polystyrenes), filtered, and vacuum-dried. After determination of the conversion via <sup>1</sup>H NMR spectroscopy, unconverted macromonomer was removed via dialysis.

**Polymer from 5a**: <sup>1</sup>H NMR (500 MHz, DMSO, 302 K): δ (ppm) = 1.08-1.68 (n\*9H, [-CH-CH<sub>2</sub>-] + αCH-(CH<sub>2</sub>)<sub>3</sub>); 2.32 (n\*2H, VBA-CO-CH<sub>2</sub>); 2.93 (n\*2H, αCH(CH<sub>2</sub>)<sub>3</sub>-CH<sub>2</sub>); 3.92 (n\*1H, αCH); 4.18 (n\*2H, VBA CH<sub>2</sub>); 4.96 (n\*4H, Z CH<sub>2</sub>); 5.97-7.05 (n\*4H, VBA arom CH); 7.17 (n\*2NH); 7.28 (n\*10H, Z arom CH); 7.95 (n\*1NH); 8.29 (n\*1NH).

**Polymer from 5b**: <sup>1</sup>H NMR (300 MHz, DMF, 298 K):  $\delta$  (ppm) = 1.12–2.01 (n\*6H,  $\alpha$ CH–(CH<sub>2</sub>)<sub>3</sub>; 2.54 (n\*2H, VBA–CO–CH<sub>2</sub>); 3.32 (n\*2H,  $\alpha$ CH(CH<sub>2</sub>)<sub>3</sub>–CH<sub>2</sub>); 4.15–4.58 (n\*3H,  $\alpha$ CH + VBA CH<sub>2</sub>); 6.17–7.31 (n\*4H, VBA arom CH); 8.31 (n\*1NH); 9.42 (n\*1NH).

**Polymer from 6a**: <sup>1</sup>H NMR (700 MHz, DMSO, 333 K):  $\delta$  (ppm) = 1.01–1.76 (n\*21H, [-CH–CH<sub>2</sub>–] +  $\alpha$ CH–(CH<sub>2</sub>)<sub>3</sub>); 2.33 (n\*2H, VBA–CO–CH<sub>2</sub>); 2.96 (n\*6H,  $\alpha$ CH(CH<sub>2</sub>)<sub>3</sub>–CH<sub>2</sub>); 3.93, 4.00 (n\*2H, outer  $\alpha$ CH); 4.23 (n\*3H, VBA–CH<sub>2</sub> + inner  $\alpha$ CH); 4.99 (n\*8H, Z CH<sub>2</sub>); 6.04–6.99 (n\*(4H + 3NH), VBA arom CH + NH); 7.12–7.55 (n\*20H, Z CH<sub>2</sub>); 7.60–7.87 (n\*3NH); 8.11 (n\*1NH).

**Polymer from 6b**: <sup>1</sup>H NMR (300 MHz, DMF, 298 K):  $\delta$  (ppm) = 1.18–2.13 (n\*18H,  $\alpha$ CH–(CH<sub>2</sub>)<sub>3</sub>; 2.49 (n\*2H, VBA–CO–CH<sub>2</sub>); 3.15 (N + 2H, VBA–COCH<sub>2</sub>–CH<sub>2</sub>); 3.31 (n\*6H,

 $\alpha CH(CH_2)_3-CH_2);\,4.25-4.67~(n^{*}5H,\,\alpha CH+VBA~CH_2);\,6.10-7.24~(n^{*}4H,\,VBA~arom~CH);\,8.03-8.55~(n^{*}NH);\,9.37~(n^{*}NH).$ 

# **Results and Discussion**

Styrene functionalized L-lysine dendrons of three different generations (5-7) were prepared by solution coupling of 4-vinylbenzylamine (1) with the appropriate  $N^{\alpha}, N^{\epsilon}$ -diprotected L-lysine dendron (2-4) under standard peptide coupling conditions (Scheme 1). The synthesis of the dendronized macromonomers was performed with an excess of 1 to drive the reaction to completion. The L-lysine functionalized macromonomers not only differed in generation but also in the chemical nature of the N-terminal protective groups. Two different protective groups were explored: the benzyloxycarbonyl (Z) and trifluoroacetyl (TFA) groups, which differ in size, polarity, and the conditions under which they can be removed. The zeroth generation dendrons (2a,b) were prepared via solution coupling of  $\beta$ -alanine-tertbutyl ester hydrochloride with the appropriate  $N^{lpha}, N^{\epsilon}$ diprotected L-lysine derivative followed by removal of the tert-butyl ester protective group. Higher generation dendrons were obtained via Fmoc solid-phase peptide synthesis. While most of the macromonomers contain  $\beta$ -alanine as a spacer between the styrene moiety and the peptide dendron, one homologue of macromonomer 7a was prepared (7c) in which 1 was directly coupled to a second generation Z-protected dendron without a  $\beta$ -alanine spacer (**4c**).

The dendronized macromonomers were characterized by means of <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy and MALDI-TOF mass spectrometry. Figure 1 shows MALDI-TOF mass spectra of the first and second generation Zprotected L-lysine dendronized macromonomers (6a and 7a, respectively). Each of the mass spectra only shows a single peak with a mass corresponding to the sodiumlabeled species. In the mass spectra, there are no indications for the presence of defects in the L-lysine dendron or for incomplete coupling of **1** to the dendron. Figure 2 shows the <sup>1</sup>H NMR spectrum of the first generation Z-protected L-lysine dendronized macromonomer (6a). Comparison of the integrals of the signals of the styrene moiety with those of the amino acid residues also indicates that the coupling reaction proceeded to completion and proves the absence of residual unreacted dendron or 1. The inset in Figure 2 shows part of the <sup>1</sup>H NMR spectrum of a batch of the same macromono-



**Figure 1.** MALDI–TOF mass spectra of macromonomers **6a** (left, m/z = 1148) and **7a** (right, m/z = 2199).

mer that was recorded prior to the washing step to remove excess and unreacted **1**. In this inset, the vinyl and methylene protons of unreacted and residual **1** appear as small peaks that are slightly shifted downfield with respect to the corresponding signals of the macromonomer.

Polymerization experiments with the  $N^{\alpha}, N^{\epsilon}$ -diprotected L-lysine dendronized macromonomers were carried out in DMF using 1 mol % 2,2'-azobis(isobutyronitrile) (AIBN) as the initiator. Earlier reports have described a strong dependence of the degree of polym-

erization of the dendronized polymers on the initial monomer concentration.<sup>13</sup> For this reason, attempts were made to investigate the polymerization of macromonomers 5-7 over a broad range of concentrations between 0.1 and 1.0 M. Of the Z-protected macromonomers 5a, 6a, 7a, and 7c only the zeroth-generation monomer (5a) was soluble in DMF at all concentrations. The first-generation monomer (6a) could not be completely dissolved in DMF at concentrations above 0.5 mol/L, and for the second-generation macromonomer 7a a homogeneous solution was obtained only at a concentration of 0.1 mol/L. Once the monomers were dissolved in DMF, the reaction mixture remained homogeneous throughout the course of the polymerization, and no precipitation was observed. In contrast to the Z-protected macromonomers, the TFA-protected macromonomers **5b** and **6b** were completely soluble in DMF at all the investigated concentrations. After a reaction time of 3 days, the polymerization mixture was precipitated in water (Z-protected L-lysine dendronized polystyrenes) or diethyl ether (TFA-protected L-lysine dendronized polystyrenes). Conversions were calculated from the <sup>1</sup>H NMR spectra of the crude reaction products by comparison of the integrals of the vinyl group of the styrene moiety with those of the amino acid residues in the L-lysine dendron (Tables 1 and 2). Subsequently, residual monomer was removed via dialysis in DMF. The purified L-lysine dendronized polymers were analyzed with <sup>1</sup>H NMR spectroscopy and GPC. The results of



**Figure 2.** <sup>1</sup>H NMR spectrum of macromonomer **6a** (300 MHz, DMSO- $d_6$ , 298 K). The inset shows part of the <sup>1</sup>H NMR spectrum of the same macromonomer prior to purification.

 Table 1. Reaction Conditions for the Polymerization of the Z-Protected Dendronized Macromonomers and GPC Results

 Obtained from the Corresponding Polymers

expt	monomer	$c_{ m monomer}^{a}$ [mol/L]	$c_{ m monomer}{}^a \ [{ m wt}\ \%]$	$\operatorname{conv}^{b}$ [%]	$M_{ m n}( imes 10^{-3})^c \ [ m g/mol]$	$\mathrm{DP}_{\mathrm{n}}^{c}$	$M_{ m w}/M_{ m n}{}^c$	$K_{ m MHKS}{}^c imes10^{-3}$	$a_{ m MHKS}{}^c$
1	5a	0.1	6.0	71	65.5	109	2.04	13.19	0.561
2		0.3	16.0	85	53.4	89	2.73	9.53	0.598
3		0.5	24.1	88	92.6	154	2.27	9.71	0.597
4		0.7	30.7	91	96.1	160	2.51	11.23	0.593
5		1	38.8	90	93.8	156	2.41	10.43	0.594
6	6a	0.1	10.6	44	60.1	53	1.88	74.32	0.381
7		0.3	26.3	62	61.5	55	2.62	12.53	0.571
8		0.5	37.3	58	104.4	93	3.57	25.42	0.495
9	7a	0.1	18.7	11	11.9	5	2.62	9553.2	0.061
10	7c	0.1	17.4	10	25.3	13	1.53	122.3	0.365

<sup>&</sup>lt;sup>*a*</sup> Initial macromonomer concentration. <sup>*b*</sup> Determined by <sup>1</sup>H NMR. <sup>*c*</sup> Number-average molecular weight ( $M_n$ ), number-average degree of polymerization (DP<sub>n</sub>), polydispersity ( $M_w/M_n$ ), and Mark-Houwink-Kuhn-Sakurada (MHKS) coefficients K and a determined from GPC.

Table 2. Reaction Conditions for the Polymerization of the TFA-Protected Dendronized Macromonomers and GPC Results Obtained from the Corresponding Polymers

expt	monomer	$c_{ m monomer}{}^a$ [mol/L]	$c_{ m monomer}^{a} \ [ m wt~\%]$	$\operatorname{conv}^{b}$ [%]	$M_{ m n}( imes 10^{-3})^c$ [g/mol]	$\mathrm{DP_n}^c$	$M_{ m w}/M_{ m n}{}^c$	$K_{ m MHKS}{}^c imes 10^{-3}$	$a_{ m MHKS}{}^c$
11	5b	0.1	5.2	91	33.3	63	2.25	8.786	0.604
12		0.3	14.2	97	45.4	87	1.86	6.061	0.644
13		0.5	21.7	98	55.9	107	1.77	5.398	0.644
14		0.7	27.9	99	77.9	149	1.61	2.215	0.729
15		1	35.6	99	67.2	128	1.88	0.919	0.784
16	6b	0.1	9.3	57	63.3	65	1.71	18.33	0.512
17		0.3	23.6	78	147.4	152	1.8	1.708	0.701
18		0.5	33.9	82	181.6	187	1.75	0.625	0.785
19		0.7	41.8	96	215.8	222	2.54	1.774	0.714
20		1	50.7	93	235.8	242	1.98	1.329	0.738

<sup>*a*</sup> Initial macromonomer concentration. <sup>*b*</sup> Determined by <sup>1</sup>H NMR. <sup>*c*</sup> Number-average molecular weight ( $M_n$ ), number-average degree of polymerization (DP<sub>n</sub>), polydispersity ( $M_w/M_n$ ), and Mark–Houwink–Kuhn–Sakurada (MHKS) coefficients K and a determined from GPC.



Figure 3. Monomer conversion vs initial monomer concentration for the Z-protected L-lysine-based dendronized macromonomers 5a, 6a, and 7a.

these experiments are listed in Tables 1 and 2 for the Z-protected and the TFA-protected dendronized polystyrenes, respectively. Figure 3 plots monomer conversion vs monomer concentration in the polymerization mixture for the Z-protected L-lysine-based macromonomers (**5a**, **6a**, **7a**).

The data in Table 1, Table 2, and Figure 3 show that monomer conversion and polymer molecular weight depend on the initial monomer concentration in the reaction medium. The effects, however, are by far not as dramatic as those reported for the polymerization of several other dendronized macromonomers.<sup>13</sup> Even at low monomer concentrations, dendronized polymers with reasonable molecular weights were obtained. Monomer conversion and polymer molecular weight decrease with increasing dendron size, which is in agreement with earlier reports on other dendronized macromonomers.<sup>1c</sup> While most polymerization experiments yielded dendronized polymers with reasonable degrees of polymerization, the second-generation Z-protected macromonomer **7a** only afforded oligomers with a numberaverage degree of polymerization according to GPC of  $\sim$ 5. Attempts to obtain higher molecular weight dendronized polymers from **7a**, e.g., by increasing the reaction time, were unsuccessful.

In addition to polymer molecular weight, the GPC experiments can also provide insight into the hydrodynamic properties of the dendronized polymers. The online coupling of a viscometer detector allows the determination of the Mark-Houwink-Kuhn-Sakurada (MHKS) coefficients K and a, which are also included in Tables 1 and 2. The MHKS coefficient a is most interesting, since its value depends on the polymer conformation. Except for the polymer obtained from 7a, the MHKS *a* coefficients are all in the range 0.5-0.8, indicative for a random coil backbone conformation.<sup>14</sup> The polymer prepared from macromonomer 7a has a very low MHKS a coefficient of 0.061, which is in the range expected for a compact sphere.<sup>14</sup> The GPC experiments, thus, suggest that at least in dilute DMF solution the zeroth and first generation dendrons are not sufficiently sterically demanding to cause stretching of the polymer backbone, and the dendronized polymers appear to adopt a random coil conformation. The very small MHKS coefficient *a* for the polymer obtained from 7a is probably related to the very small degree of polymerization of this polymer. It is also difficult to evaluate the effect of the introduction of the  $\beta$ -alanine spacer on the backbone conformation of the dendronized polymers. The difference in the MHKS coefficient a



**Figure 4.** (a) TEM micrograph of an ultrasharp Hi'Res AFM tip with a radius  $\leq 3 \text{ nm}$ . (b–e) AFM images of dendronized polymers obtained by polymerization of macromonomer **6a** at a concentration of 0.1 mol/L (b), macromonomer **6a** at a concentration of 0.5 mol/L (c, e), and macromonomer **7a** (d). Samples were prepared by spin-casting onto mica substrates.

between samples **7a** and **7c** cannot be directly attributed to the presence/absence of the  $\beta$ -alanine spacer since the two polymers have significantly different molecular weights.

In an attempt to obtain additional insight into the structure of the dendronized polymers, AFM experiments were performed on thin films, which were spincast from DMF on mica substrates. Obtaining highresolution images of the samples proved difficult and took significant effort; however, using ultrasharp tips, single molecule resolution could be achieved. So far, only images from dendronized polymers based on macromonomers 6a and 7a could be obtained. Figure 4 shows images obtained from dendronized polymers prepared by polymerization of **6a** at concentrations of 0.1 and 0.5 mol/L and 7a at 0.1 mol/L. The image with the highest resolution is Figure 4c, which shows rodlike objects. Analysis of an ensemble of 100 molecules in Figure 4c revealed an average length of  $15\pm7$  nm and an average diameter of 6.6  $\pm$  1.3 nm. The length of the rods is close to that expected for an extended backbone conformation assuming a length of 0.25 nm per styrene repeat unit and a degree of polymerization of  $\sim 90$ . Although the resolution is not as good as in Figure 4c, the images in Figure 4b and Figure 4d reveal short rodlike objects and globular structures, respectively. Since the samples imaged in Figure 4b and Figure 4d have degrees of polymerization of  $\sim 50$  and  $\sim 5$ , which is much smaller than that of the sample shown in Figure 4c, this illustrates the effect of the degree of polymerization on the single molecule structure of these peptide dendronized polymers.

At a first glance, the results from the GPC experiments and the AFM images seem contradictionary. While the MHKS *a* coefficients suggest a random coil backbone conformation, the AFM images reveal rodlike structures for the polymers prepared from macromonomer **6a**. One explanation for this discrepancy may be the moderate degrees of polymerization of the dendronized polymers. The polymer obtained from **6a** at a monomer concentration of 0.5 mol/L has a number-average degree of polymerization of ~90, which is in good agreement with the observed rod length of ~15  $\pm$  7 nm, assuming a length of 0.25 nm per styrene repeat

unit and an almost extended backbone conformation. However, since the diameter of the rods is  $\sim$ 6.6 nm, the aspect ratio of the objects is relatively small, and the hydrodynamic behavior of the molecules may rather approximate that of a compact sphere or ellipsoid instead of a rod.

## Conclusions

In this contribution, we have described the synthesis of a new class of peptide dendronized polymers, which were obtained via free radical polymerization of styrene functionalized L-lysine dendrons. While the dendronized macromonomers of the zeroth and first generation generally afforded high molecular weight dendronized polymers (number-average degree of polymerization (DP): 50-240), only short oligomers (DP = 5-10) were obtained for the second generation macromonomers. First AFM experiments illustrated the effect of the degree of polymerization on the single molecule architecture; with decreasing degree of polymerization, the structure of the dendronized polymers changes from rods to short rods to globules. Extensive studies to elucidate the structure of the materials are underway and will be reported elsewhere.

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