Peptidic Molecular Brushes with Enhanced Chirality

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Received 30 January 2012; accepted 6 June 2012; published online
DOI: 10.1002/pola.26208

ABSTRACT: Tethering oligopeptides through one end densely packed onto a linear polymer main chain will greatly reduce freedom of the peptide chains, which affords an easy access to investigate the secondary structure of peptides under constrained condition. Herein, molecular brushes with densely grafted monodispersed Cbz-protected oligolysine were efficiently synthesized via free radical polymerization of the macromonomer-bearing lysine octamer, and the secondary structures of the oligopeptide side chains in solutions were investigated. To examine the architecture effects on helical conformation, circular dichroism spectra from the polymer were compared with that from the corresponding macromonomer. To check the chemical structural effects on conformation of the oligopeptide, Cbz groups from the molecular brushes were deprotected, and the secondary structures of the polymers were compared before and after the deprotection. Conformation of the deprotected polymer was further explored by varying solution pH values. Complexation of the positively charged, deprotected polymer with anionic surfactant provides an alternative route to mediate the secondary structures of the short peptides in the constrained environment. It has been found that oligolysine side chains within the molecular brushes can adopt enhanced α-helical conformation through the crowding structures or can form β-sheet by hydrophobic interactions between the complexed surfactants. © 2012 Wiley Periodicals, Inc. J Polym Sci Part A: Polym Chem 000: 000–000, 2012

KEYWORDS: branched; free radical polymerization; macromonomers; peptides; secondary structures

INTRODUCTION Ordered secondary structures of peptides in nature, such as α-helices and β-sheets, play crucial role in forming organized tertiary structures of proteins, which dominate their functions and properties as well as their biological activities. On one hand, the stabilization of these secondary conformations will not only guarantee the proper activities of the proteins but also prevent them from forming abnormal amyloid fiber aggregates, which is the key issue to cause the fatal diseases like Alzheimer's and Parkinson's diseases.[1] On the other hand, enhancement of the chirality may also promote the ordered structural formation, which facilitates the biological functions of the proteins. By mimicking these peptides in nature, to synthesize (poly)peptides with ordered secondary structures will be interesting for both fundamental researches and for applications ranging from biomaterials to biotechnology. Up to date, synthetic polypeptides of different architectures have been reported, including linear,[2] cyclic,[3] branched,[4] star-like,[5] dendritic,[6] and comblike ones,[7] and the stability of their secondary conformation has been widely explored. Much effort have been devoted to investigate the secondary structures of synthetic polypeptides in free forms, and less attention was paid to the architecture effect on their chirality enhancement.[8,9] In general, α-helical conformation is stabilized mainly by the intramolecular amide hydrogen bonds, whereas the stability of β-sheet is dependent mostly on hydrophobic interactions between amino acid residues.[10] One specific parameter showing strong influence on the secondary structures of a peptide is its chain length. It is well known that α-helix is stabilized by increasing peptide chain length,[11] whereas parallel[12] and antiparallel β-sheets[13] show different dependence on their peptide lengths or the intrinsic strand lengths. In nature, about 30% of proteins contain peptide sequences of less than 15–25 amino acids, which often mediate biological processes through their ordered secondary structures to interact with proteins, DNA, or RNA.[14] In contrast, short synthetic peptides corresponding to these recognition motifs generally adopt random coil structures or low populations of ordered conformations in water. Therefore, to mimic and stabilize the ordered secondary structures of short peptides[15] are valuable to understand their roles in protein folding and in mediating their interactions with biomacromolecules and may lead to the development of novel pharmaceuticals, vaccines, and diagnostics.

Molecular brushes are a novel class of cylindrical polymers with linear side chains densely pendent onto a linear polymer main chain.[16] The structural characteristics of these

Additional Supporting Information may be found in the online version of this article.

polymers include high rigidity and large persistent length, versatile chemical structure variability, and the nanosized dimension of individual molecule. The steric repulsion between the densely packed side chains enhances stiffness of the backbone and, at the same time, may mediate different behavior of the side chains. Based on these factors, molecular brushes have gathered intense research attention and been applied in many areas.[17] This kind of polymers can be synthesized mainly through macromonomer "grafting from" and "grafting onto" routes.[16(c),18] Among them, macromonomer route often provides the targeted polymers with relatively defined chemical structures. Up to now, most of the reported molecular brushes contain polydispersed side chains, which to certain degree destroy the regularity of the polymer structures. One intriguing class of molecular brushes is that polypeptides are combined, which will not only afford the polymer biorelated functions but also may combine the possible secondary structures from polypeptides into the bulky polymers. One way is to use polypeptide as the main chain and other polymers as the side chains, and it was found that the secondary structures of polypeptide main chain are dependent on the size of the side chain.[7(f)] Another way is to use polypeptide as side chains but the other polymers as the main chain. For example, Emrick and coworkers reported the synthesis of polyolefin-*graft*-oligolysine polyelectrolytes by the combination of solid-phase peptide synthesis and ring-opening metathesis polymerization and that found the polyelectrolytes could be tailored to form extended, pearl-like, or multimolecular structures, depending on the composition and density of the peptide grafts.[19] Schmidt and coworkers reported cylindrical molecular brushes with densely grafted poly(L-lysine) or poly(L-glutamate) side chains, and both macromonomer and grafting from routes were applied and compared. The latter route was shown to be more successful for the synthesis of cylindrical brushes with high molar mass main and long side chains.[20] Interestingly, these positively charged peptidic molecular brushes after deprotection can form large pitch helices by complexation with anionic surfactants.[21] Improved technique for polymerization of amino acid *N*-carboxyanhydride (NCA) was used by Cheng and coworkers to prepare peptidic molecular brushes with better defined structures.[22] By one-pot synthesis of side-chain peptide brushes via the combination of ring-opening metathesis polymerization and ring-opening polymerization of NCA, the polymers with controlled molecular weight were achieved, and their molecular weight distribution (MWD) is relatively low. These peptidic brushes alone can form ordered helices at neutral condition through aggregation.[23] Because of the synthetic challenges, the architecture effects on the conformational structures of grafted polypeptides have not been systematically studied in the brush-like (co)polymers. Recently, Cheng and coworkers reported on a class of brush-like polymers grafted with polylysines and interestingly found that grafted architecture showed positive effects on stabilizing the ordered secondary structures of the polylysine side chains when the polymerization degree of the side chains is less than 100; however, this positive effect vanished for the case with the longer polypeptide side chains because of the strong interchain hydrogen bonding disruption.[24]

One common feature of most peptidic molecular brushes is that the peptide side chains are polydispersed. No matter how big or small their MWDs are, this polydispersity leads to irregular structures to certain degree and often causes the solubility[20] or aggregation[23] problems. To avoid this, we recently reported on peptidic molecular brushes with monodispersed proline octamer as the side chains through macromonomer route.[25] Oligoproline was selected because of the consideration that polyprolines can adopt two different helical conformations: compact polyproline I (PPI) and stretched polyproline II (PPII). The former is favored in less polar solvents such as alcohols, whereas the latter is favored in polar solvents such as water. These two distinguished conformations are interexchangeable by *cis–trans* isomerization of the peptide bonds. Because of the dense packing of rigid proline octamer along the polymer main chain within the molecular brush, the oligoproline side chains can only adopt the more stretched PPII conformation no matter what solvents were used, and the helical conformation transition from PPII to PPI was completely hindered. In this work, a novel class of molecular brush with well-defined oligopeptide side chains is also prepared via macromonomer route. It is constructed by a polymethacrylate main chain and monodispersed lysine octamer side chains (Fig. 1). Oligolysine is selected here because polylysines can adopt three different conformations at certain conditions: α-helix, β-sheet, and random coil. This system is designed to investigate whether such short lysine peptides may show ordered conformation under this constrained condition, and how these conformations will be influenced by external condition changes.

RESULTS AND DISCUSSION

Synthesis and Characterization

Oligolysines were prepared via typical solution amidation conditions as shown in Scheme 1. Boc and Cbz are selected as orthogonal protection groups for easy synthesis manipulation, and Cbz protecting group along the oligopeptide chain is selected for the purpose to examine possible influence of π–π interaction on the peptide secondary conformation within the molecular brushes. Starting from commercially available H-Lys(Cbz)-OMe and Boc-Lys(Cbz)-OSu, the amide coupling was readily performed in the presence of diisopropylethylamine (DiPEA) at -15°C, providing dipeptide ester **1a** with a yield of 96%. Hydrolysis of **1a** formed the acid **1b**, which was reacted with 4-nitrophenol to form the active ester **1c**. It was found that the purification of **1c** with silica gel column chromatography did not work. Most probably because of the high reactivity of the dipeptide active ester, majority of the products reacted with the silicon gel and stayed inside the column. Instead, **1c** was purified just by precipitation into hexane/ethyl acetate. Deprotection of the dipeptide ester with trifluoroacetic acid (TFA) afforded quantitatively the ammonium salt **1d**. Amide coupling of **1c** with **1d** furnished the tetrapeptide ester **2a**. During the reaction, a gel-like solution was formed, which indicates the lower

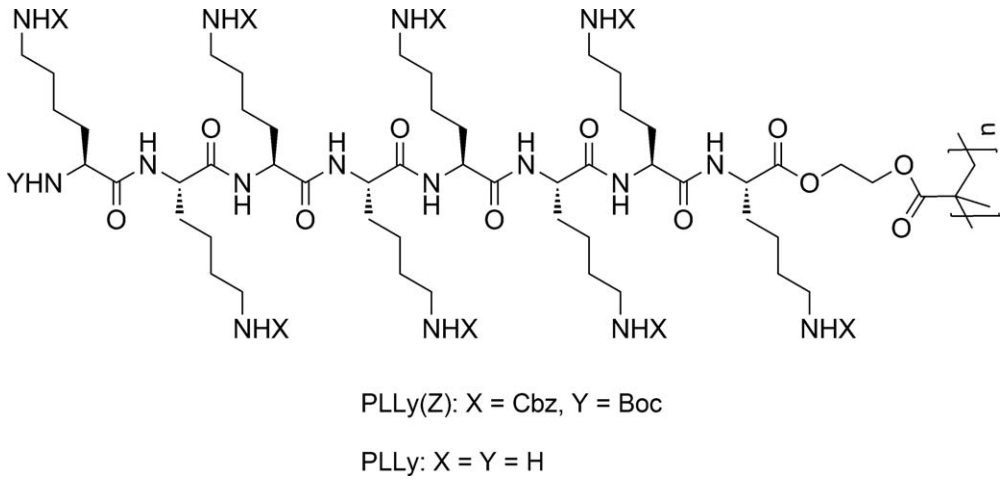
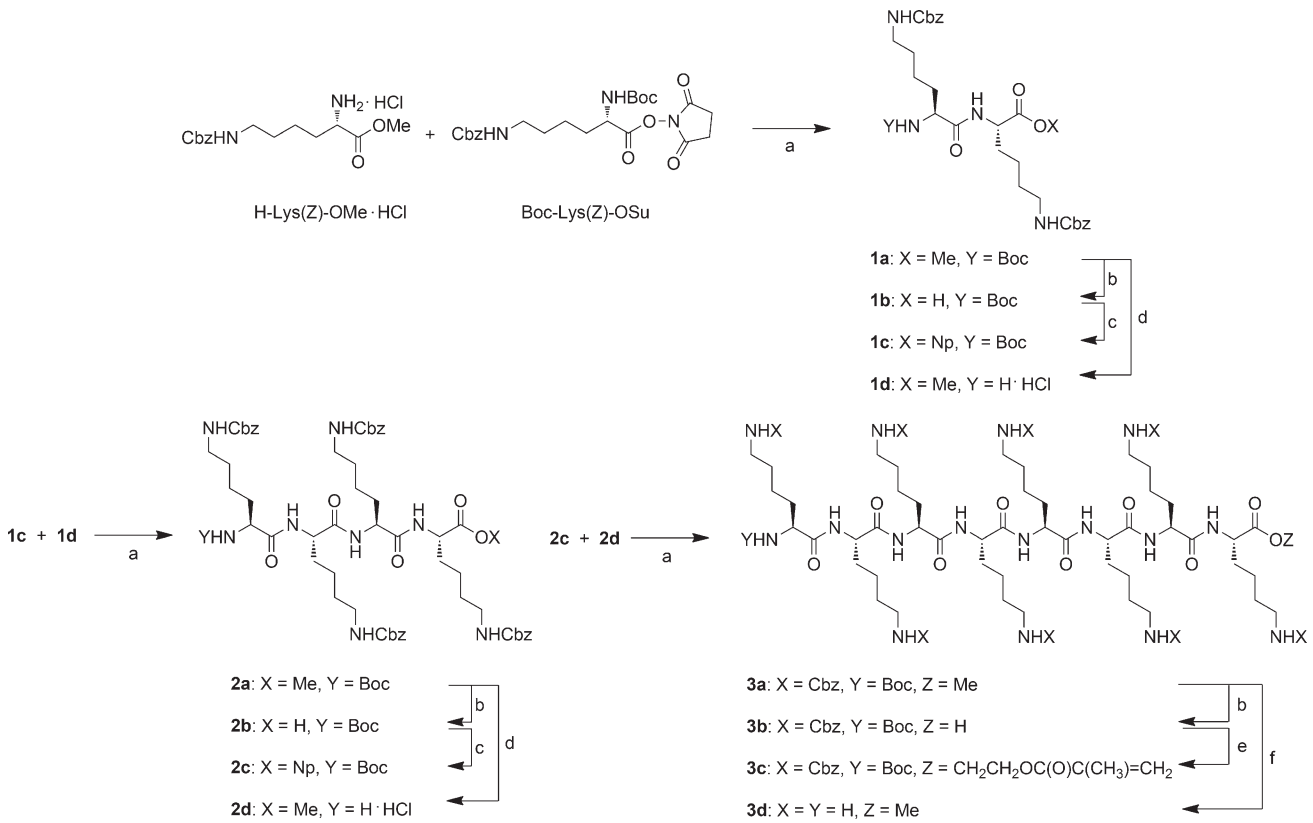


FIGURE 1 Chemical structures of the molecular brushes with monodispersed oligolysine side chains reported in this work.

solubility of **2a** in dichloromethane (DCM) due to the strong hydrogen bonding.[26] Therefore, small amount of MeOH was mixed with DCM to improve the solubility during the work up. Through column chromatography, **2a** was obtained in a yield of 92%. By similar procedures, **2a** was converted into the active ester **2c** and the corresponding ammonium salt **2d**. Finally, the octamer ester **3a** was achieved in 85% yield by the amide coupling of **2c** with **2d**. Saponification with



SCHEME 1 Synthesis procedure of oligolysines and the macromonomer. Reagents and conditions: (a) DiPEA, DCM, DMF, −15°C - room temperature, overnight (96, 92, or 85%); (b) LiOH·H_2O, THF, MeOH, H_2O, 0°C - room temperature, 6–8 h (98 or 99%); (c) EDC, Np—OH, DCM, −10°C - room temperature, overnight (93 or 94%); (d) TFA, DCM, 0°C - room temperature, overnight (100%); (e) HEMA, EDC, DMAP, DCM, 0°C - room temperature, overnight (74%); (f) HBr, TFA, room temperature, 1 h (93%). Abbreviations: AIBN, azobis(isobutyronitrile); DCM, dichloromethane; DMAP, 4-*N, N*-dimethylaminopyridine; DiPEA, diisopropylethylamine; DMF, *N, N*-dimethylformamide; EDC, 1-(3-dimethylaminopropyl)-3-ethylcarbo-diimide hydrochloride; HEMA, 2-hydroxyethyl methacrylate; Np—OH, *para*-nitrophenol; TEA, triethylamine; TFA, trifluoroacetic acid.

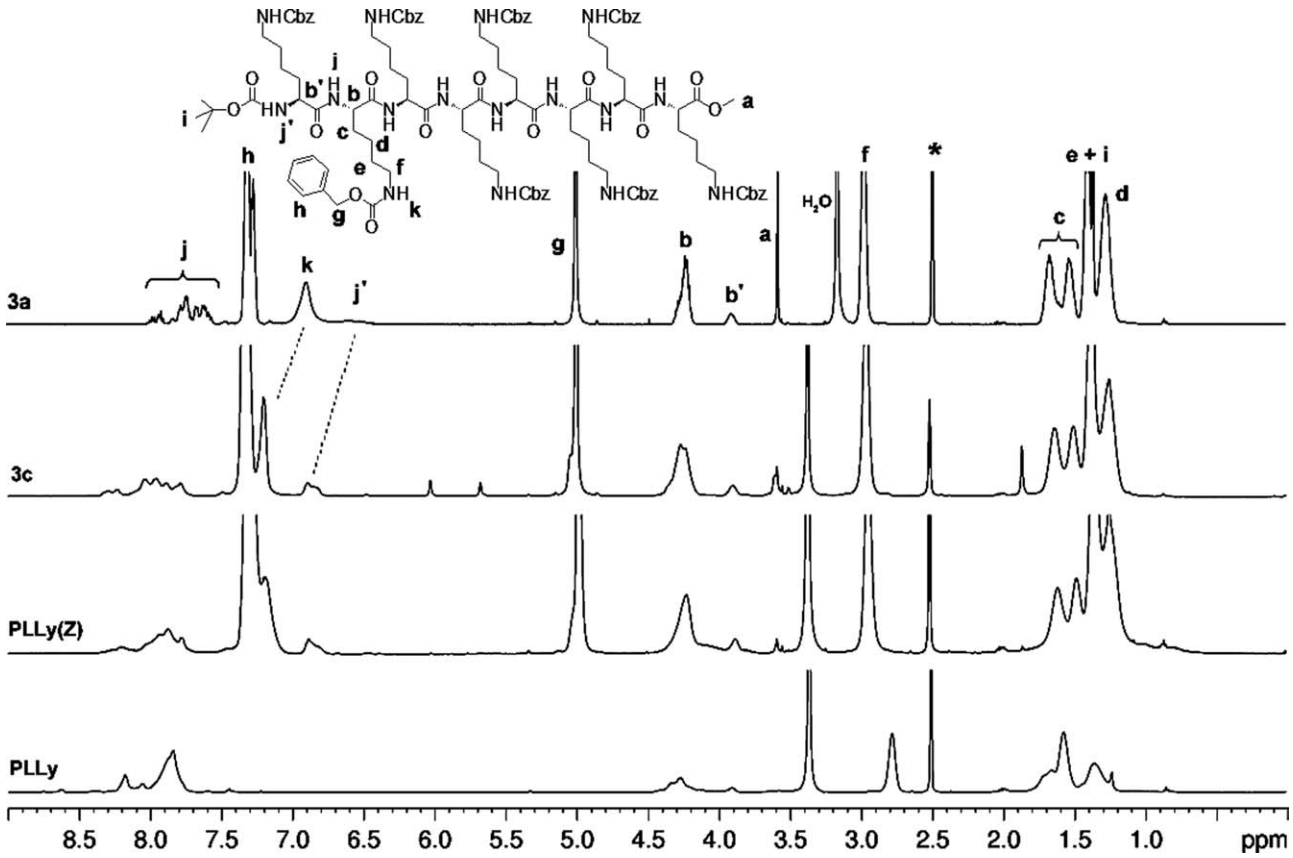


FIGURE 2 ^{1}H NMR spectra of compound **3a** (at 60°C for better resolution), macromonomer **3c**, and the corresponding polymers PLLy(*Z*) and PLLy in [d]$_6$-DMSO. *The signal from solvent [d]$_6$-DMSO. The dot lines are a guide for the eyes.

LiOH formed the octamer acid **3b**, which was reacted with 2-hydroxyethyl methacrylate (HEMA) in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbo-diimide hydrochloride (EDC) to afford the macromonomer **3c**. EDC was selected here for the esterification as it produced water-soluble byproduct, which can be easily washed away to guarantee the high purity of the macromonomer. It is worthwhile to note that when compared with the tetramers, all the octamers formed higher viscous solutions in DCM. Once evaporating **3c** in DCM to dryness, the macromonomer became gel and was not able to be dissolved anymore in various solvents even like MeOH or *N, N*-dimethylformamide (DMF). To avoid this, a mixture of MeOH with DCM was used for dissolving **3c** at the beginning to achieve a dilute solution. Evaporation to dryness from this mixed solvent **3c** was obtained as a white powder, which was soluble and can be used for polymerization. All new compounds except the active esters were characterized as analytically pure materials by ^{1}H and ^{13}C NMR spectroscopy, as well as high-resolution mass spectroscopy. Typical ^{1}H NMR spectra of the octamer ester **3a** and macromonomer **3c** in [d_6]-DMSO are shown in Figure 2. The chemical shift assignments of **3a** were based on the ^{1}H-^{1}H COSY spectrum from Supporting Information Figure S17.

Conventional free radical polymerization of macromonomer **3c** in DMF in the presence of azobis(isobutyronitrile) (AIBN) as initiator at 65°C afforded the molecular brush PLLy(*Z*). This polymer is soluble in DMF, DMSO, or the mixed solution like THF/MeOH, but cannot be dissolved even at elevated temperature in other single solvent including DCM, MeOH, and THF. The molar mass (M_n) of the polymer was determined by gel permeation chromatography (GPC) with DMF as the eluent. Surprisingly, the M_n is 2.0×10^4 (relative to PMMA standards), which is not as high as expected, and the PDI is extremely small (1.2). Such narrow PDI is unusual for polymers synthesized via conventional free radical polymerization. The possible reason for these results is that densely packed architecture within the molecular brush affords the polymer with high rigidity, which leads to the underestimation of M_n and the abnormal PDI by GPC measurements. Similar observation has also been reported for other bulky polymers.[27] Dynamic light scattering (DLS) measurements of the polymer in MeOH/THF (v/v = 1:1) show that R_h of the polymer is around 23 nm (Supporting Information Fig. S2), which also suggests that the polymer possesses high molecular weight. To achieve the water-soluble peptidic molecular brushes, the Cbz-protected polymer PLLy(*Z*) was dissolved in TFA and deprotected by HBr (33% in acetic acid) to afford the polymer PLLy. The ^{1}H NMR spectra of both polymers are shown in Figure 2. In comparison of the spectra for these protected and deprotected polymers, the disappearance of the signals at δ = 7.3–7.4 and δ = 4.9–5.1 from the Cbz groups illustrates the

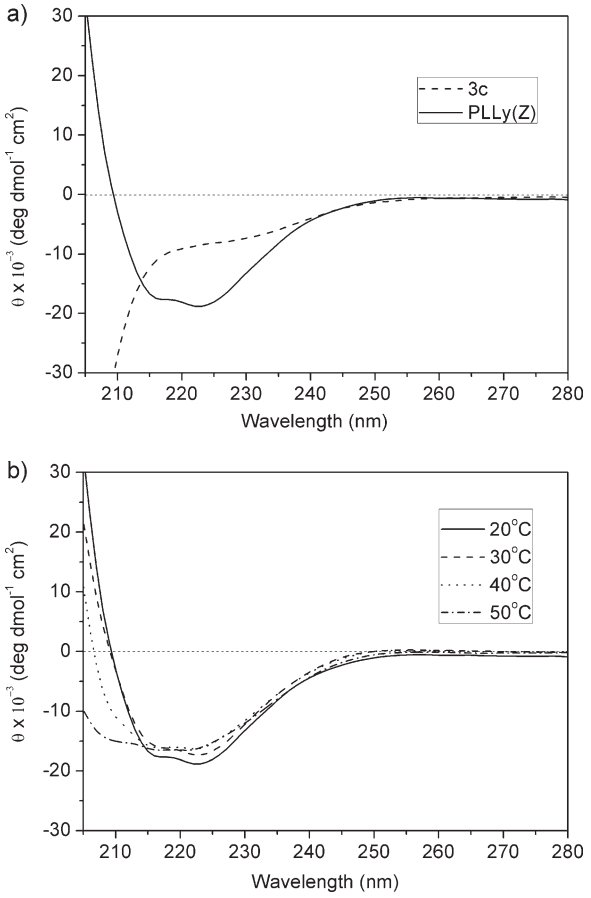


FIGURE 3 CD spectra of macromonomer **3c** and PLLy(*Z*) in THF/MeOH (v/v = 1:1.4) at 20°C (a) and of PLLy(*Z*) at different temperature (b).

successful deprotection of Cbz groups. Interestingly, the spectrum of the monomer is reminiscence very much of that of the polymers regarding the peak broadness, most probably due to the weak solubility of the monomer.

Secondary Structure Analysis

Optical rotation spectroscopy (OR) and circular dichroism spectroscopy (CD) were applied to examine the secondary structure of the polymers in solution. For comparison, the macromonomer was also measured. Because of the solubility reason, MeOH/THF mixed solvent was chosen for the measurements. The OR from the polymer PLLy(*Z*) is $+122^{\circ}$, which is quite different from that of the macromonomer (OR = -3°). This big difference indicates that the polymer possesses much higher order structures than the corresponding macromonomer. The CD spectra for both the macromonomer and PLLy(*Z*) are shown in Figure 3(a). As expected for a short peptide, the CD spectrum from the macromonomer indicates that it adopts minimal ordered secondary structure in solution. In contrast, polymer PLLy(*Z*) exhibits strong Cotton effects with two negative peaks in the wavelength of 221 and 216 nm, which resembles the characteristics of the α-helical conformation of peptides. The red shift from 209 to 216 nm for one of the two minima should be mainly related to the solvent effects.[28] The different Cotton effect from the macromonomer and the polymer proves that the ordered secondary structure within the molecular brush should be caused by the densely packing of the side peptide chains, and this architecture may enhance carbamate hydrogen bonding between lysine side chains and the π–π stacking between the aromatic rings from the Cbz groups, which induce the side chains to adopt more ordered structures. Similar observation has also been reported by Cheng and coworkers[24] in brush-like polymers when polymerization degree of the side-chain polylysines is less than 100. The influence of the temperature on the helical conformation stability of PLLy(*Z*) was also examined [Fig. 3(b)]. When the temperature increased from room temperature to 40°C, the helicity decreased slightly (ellipticity at 221 nm decreases from 17,300° to 14,700°). However, when solution temperature further increased to 50°C, the CD curve changed its shape and that the minimum peak blue-shifted from 216 to the normal position (210 nm). The change of curve shape suggests that the oligopeptides show tendency to transfer from α-helix into β-sheet with temperature.

To examine the architecture effects on the ordered secondary structure of peptide side chains, PLLy(*Z*) is deprotected into PLLy, and its conformation in aqueous solution was thus investigated with CD spectroscopy, and the spectra are shown in Figure 4(a). At pH 7 when peptides are positively

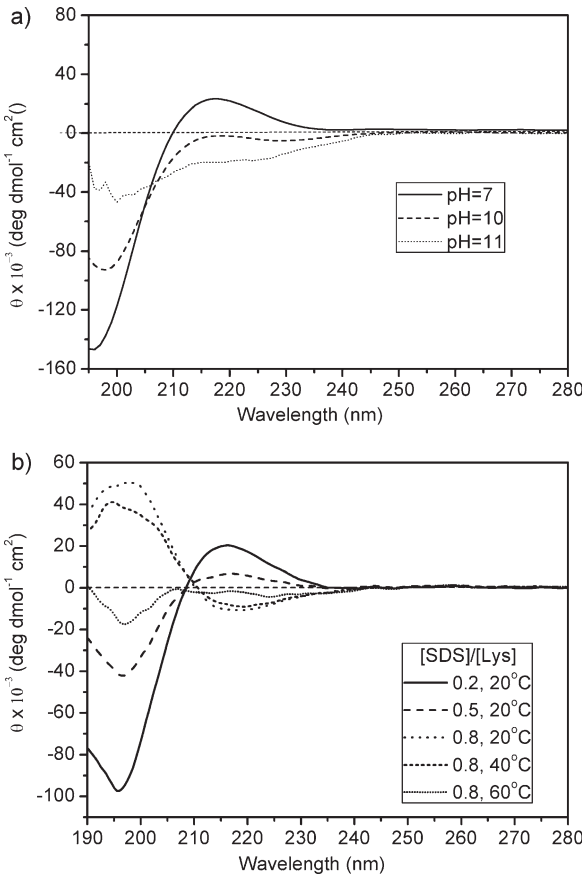


FIGURE 4 CD spectra of PLLy in water without (a) and with SDS (b). [SDS]/[Lys] represents the molar ratio of SDS to lysine unit within the deprotected polymer.

charged, typical Cotton effect of random coil conformation was obtained as expected. Even when solution pH was increased to strong basic conditions such as 10 or 11 when lysine units are not protonated, the CD spectra of the molecular brush are again reminiscent mainly of random coil with very low population of ordered structures (α-helix and β-sheet).[10] This is in contrast to that deprotonated polylysines of long chains can adopt α-helical conformation with intramolecular hydrogen bonding interaction between repeating units of i and $i + 3$. The above results suggest that the closely packed architecture of short peptides cannot guarantee the formation of the well-ordered secondary structure and that the structural effects in polymer PLLy(Z) should come from carbamate hydrogen bonding between lysine side chains and the π–π stacking between the aromatic rings from the Cbz groups within the proximately packed peptide chains.

It is well known that free polypeptide chains can vary their conformation at neutral condition in the presence of ionic or amphiphilic species. For example, the conformation of high molar mass polylysines can be transformed from random coil into α-helix by sodium octyl sulfate or into β-sheet by sodium dodecyl sulfate (SDS) because of the hydrophobic interaction between the bounded surfactants that dominates over the electrostatic interaction among the lysine units.[29] In the case of molecular brushes, oligopeptide chains are end-tethered on the main chain with less freedom, and therefore, we are curious to see whether the very short peptide chains within the molecular brush would adopt ordered secondary structures on complexation with ionic surfactants. Herein, SDS salt was complexed with PLLy in different ratios in aqueous solutions at pH 7, and the conformation was investigated by CD spectroscopy. From CD spectra in Figure 4(b), it is observed that the peptide chains changed their conformation gradually with the increase of SDS ratio at room temperature. When the molar ratio of SDS/lysine unit reached 0.8/1, the CD spectrum exhibits a minimum at 217 nm and one maximum below 200 nm, which suggests that the short peptide chains adopt β-sheet conformation. From the ellipticity at 217 nm, the content of peptide chains adopting β-sheet conformation is estimated to be 70–80% according to method proposed by Davidson Fasman.[10] Further increase of the ratio to 1.0 led to the precipitation of the polymers from aqueous solution. This β-sheet conformation is thermally unstable, and the content decreases with the increase of solution temperature. When the solution temperature increased to 60°C, the ordered structure was mostly lost. For comparison, the CD spectra from deprotected octamer **3d** and its complexation with SDS were also recorded (Supporting Information Fig. S1). The deprotected octamer itself in aqueous solution adopts random coil structure, and this random conformation retains even with the addition of SDS. This control experiment further supports that the brush architecture shows positive effect on stabilization of ordered structures from oligopeptides.

CONCLUSIONS

We present here the efficient synthesis and conformation characterization of molecular brushes that were constructed by a polymethacrylate main chain and monodispersed lysine-based oligopeptide side chains. Their secondary structures were investigated with OR and CD spectroscopy. This molecular brush architecture affords the short peptide side chains a constrained environment to adopt enhanced chirality. When Cbz protection group is present, carbamate hydrogen bonding and π–π stacking between the aromatic rings within the proximately packed peptide chains promoted the α-helical conformation of oligopeptides in solutions at various temperatures. After deprotection, the helical conformation of the peptides was mostly lost even at basic conditions; however, the ordered β-sheet conformation of these short peptide side chains can be easily formed by complexation with surfactants such as SDS. With increased amount of SDS, the propensity to form this ordered structure was enhanced. This work demonstrates that the molecular brush architecture offers a constrained environment that can stabilize and enhance the ordered secondary structures of oligopeptides.

EXPERIMENTAL

Materials

AIBN was recrystallized twice from methanol. DCM was distilled from CaH_2 for drying. Other reagents and solvents were purchased at reagent grade and used without further purification. All reactions were run under a nitrogen atmosphere. Macherey-Nagel precoated thin-layer chromatography (TLC) plates (silica gel 60 G/UV254, 0.25 mm) were used for TLC analysis. Silica gel 60M (Macherey-Nagel, 0.04–0.063 mm, 200–300 mesh) was used as the stationary phase for column chromatography.

Instrumentation and Measurements

Proton and carbon NMR spectra were recorded on Bruker AV 500 (^{1}H: 500 MHz, ^{13}C: 125 MHz) spectrometers at room temperature (unless indicated), and chemical shifts are reported as δ values (ppm) relative to internal Me_4Si. High-resolution ESI-MS analyses were performed on IonSpec Ultra instruments. GPC measurements were carried out on a Waters GPC e2695 instrument with three-column set (Styragel HR3+HR4+HR5) equipped with refractive index detector (Waters 2414) and DMF (containing 1 g L^{-1} LiBr) as eluent at 45°C. The calibration was performed with poly(methyl methacrylate) standards in the range of M_p = 2580–981,000 (Polymer Standards Service USA). DLS measurements were performed on an ALV/DLS/SLS-5022F spectrometer equipped with a multi-τ digital time correlation (ALV5000) and a cylindrical 22-mW He–Ne laser (λ_0 = 632 nm, UNIPHASE) as the light source, and the sample concentration is 0.66 mgmL^{-1} in THF/MeOH (v/v = 1:1). CD measurements were performed on a JASCO J-815 spectropolarimeter with a thermocontrolled 1-mm quartz cell (five accumulations, continues scanning mode, scanning speed: 50 nmmin^{-1}, data pitch: 1 nm, response: 1 s, band width: 5.0 nm). Monomer and protected polymer samples were dissolved in mixed solvents from THF and methanol (volume ratio = 1:1.4), whereas the deprotected polymer samples were dissolved in buffer with different pH value. The concentrations used are in the range of $1-2 \times 10^{-6}$ dmol mL^{-1}. OR measurements

were also performed on the JASCO J-815 spectropolarimeter (wavelength = 589 nm) at 20°C with sample concentrations in the range of 1.00–1.20 $mgmL^{-1}$. The complexation of PLLy with SDS was conducted by adding desired amount of SDS aqueous solution (1 $mgmL^{-1}$) dropwise into the PLLy aqueous solution (0.24 $mgmL^{-1}$) under vigorous stirring at pH 7.

Synthesis

Compound 1a

A solution of Boc-Lys(*Z*)-OSu (10.00 g, 20.94 mmol) in dry DCM (50 mL) was dropped into a mixture of H-Lys(*Z*)-OMe·HCl (7.62 g, 23.03 mmol) and DiPEA (10.82 g, 83.76 mmol) in DMF (30 mL) at −15°C in 30 min. The solution was allowed to warm at room temperature and stirred for another 12 h. The mixture was washed with brine, and then the aqueous phase was extracted with DCM three times. The combined organic phases were dried over $MgSO_4$. Purification with column chromatography using ethyl acetate/hexane (1:2 and 1:1, v/v) afforded **1a** (13.20 g, 96%) as white foam.

^{1}H NMR ($CDCl_3$): δ = 1.32–1.85 (m, 21H, CH_2+CH_3), 3.10–3.18 (m, 4H, CH_2), 3.66 (s, 3H, CH_3), 4.13–4.14 (m, 1H, CH), 4.51–4.52 (m, 1H, CH), 5.07 (s, 4H, CH_2), 5.40 (br, 1H, NH), 6.85 (br, 1H, NH), 7.17–7.49 (m, 10H, CH). ^{13}C NMR ($CDCl_3$): δ = 22.62, 22.67, 28.72, 29.52, 29.76, 31.96, 31.98, 32.22, 32.24, 40.75, 52.26, 52.80, 54.57, 54.60, 67.03, 67.11, 80.45, 80.48, 128.48, 128.54, 128.58, 128.90, 128.99, 136.95, 137.03, 157.00, 157.02, 172.61, 173.00. HRMS (ESI): *m/z* calcd. for $C_{34}H_{48}N_4O_9Na$ $[M+Na]^+$ 679.3314; found: 679.3323.

Compound 1b

1a (8.50 g, 12.93 mmol) was dissolved in a solution of THF (120 mL), MeOH (100 mL), and water (30 mL). $LiOH·H_2O$ (2.72 g, 64.65 mmol) was then added in one portion at 0°C. The reaction was stirred at room temperature for another 7 h. The solvents were evaporated *in vacuo* at room temperature, and the residue was dissolved with DCM. The pH value of the solution was adjusted carefully to around 3–5 with 10% $KHSO_4$ aqueous solution. The aqueous phase was extracted with DCM three times. The combined organic phase was washed with brine and dried over $MgSO_4$. After filtration, evaporation of solvents *in vacuo* afforded **2a** (8.2 g, 98%) as white foam, which was used directly for the next reaction.

^{1}H NMR ($CDCl_3$): δ = 1.39–1.86 (m, 21H, CH_2+CH_3), 3.10–3.12 (m, 4H, CH_2), 3.97–4.17 (m, 1H, CH), 4.52–4.4.61 (m, 1H, CH), 5.06–5.54 (m, 5H, CH_2+NH), 5.99–6.23 (m, 1H, NH), 7.18–7.32 (m, 10H, CH). ^{13}C NMR ($CDCl_3$): δ = 22.39, 28.45, 29.29, 29.47, 31.05, 31.42, 32.12, 40.60, 40.71, 52.18, 54.31, 66.83, 67.26, 80.24, 128.04, 128.24, 128.64, 136.72, 156.09, 156.92, 172.82. HRMS (ESI): *m/z* calcd. for $C_{33}H_{46}N_4O_9Na$ $[M+Na]^+$ 665.3157; found: 665.3174.

Compound 1c

EDC (3.67 g, 19.18 mmol) was added into a solution of **1b** (8.22 g, 12.79 mmol) and *para*-nitrophenol (Np—OH; 2.67 g, 19.18 mmol) in DCM (150 mL) at −10°C. After stirring overnight at room temperature, the mixture was washed with water and extracted with DCM three times. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was then precipitated into hexane/ethyl acetate (2:1, v/v), and then the solid was collected. Further drying of the solid *in vacuo* afforded **1c** (9.10 g, 93%) as a slight yellow foam, which was used directly for the next reaction.

^{1}H NMR ($CDCl_3$): δ = 1.41–1.66 (m, 17H, CH_2+CH_3), 1.81–2.00 (m, 4H, CH_2), 3.15–3.26 (m, 4H, CH_2), 4.11–4.17 (m, 1H, CH), 4.68–4.72 (m, 1H, CH), 4.94 (br, 1H, NH), 5.06–5.18 (m, 4H, CH_2), 7.02–7.14 (d, 1H, NH), 7.26–7.34 (m, 12H, CH), 8.21–8.24 (m, 2H, CH). ^{13}C NMR ($CDCl_3$): δ = 22.76, 28.68, 28.72, 29.74, 29.90, 31.26, 31.46, 32.07, 40.44, 40.60, 40.69, 52.76, 52.87, 54.45, 67.05, 67.11, 67.24, 80.75, 122.68, 122.72, 125.66, 125.68, 128.46, 128.53, 128.58, 128.93, 136.83, 136.94, 136.96, 145.97, 155.48, 156.26, 157.04, 157.15, 157.27, 170.36, 170.42, 172.96, 173.19. HRMS (ESI): *m/z* calcd. for $C_{39}H_{50}N_5O_{11}$ $[H]^+$ 764.3501; found: 764.3478.

Compound 1d

TFA (8.50 g, 74.50 mmol) was added into a solution of **1a** (4.70 g, 7.08 mmol) in DCM (40 mL) at 0°C, and the mixture was stirred overnight at room temperature. MeOH was added to quench the reaction. Evaporation of all the solvents afforded **1d** as a slightly yellow oil (4.80 g, 100%).

^{1}H NMR (CD_3OD): δ = 1.51–1.58 (m, 8H, CH_2), 1.70–1.76 (m, 2H, CH_2), 1.86–1.90 (m, 2H, CH_2), 3.09–3.17 (m, 4H, CH_2), 3.66 (s, 3H, CH_3), 3.85–3.88 (m, 1H, CH), 4.40–4.43 (m, 1H, CH), 5.05 (s, 4H, CH_2), 7.28–7.33 (m, 10H, CH). ^{13}C NMR (CD_3OD): δ = 21.66, 23.00, 29.40, 29.47, 30.84, 31.23, 40.24, 40.40, 51.83, 52.08, 53.20, 53.26, 53.44, 53.62, 66.37, 66.45, 111.65, 113.92, 116.18, 118.44, 127.73, 127.80, 127.98, 128.01, 128.48, 137.35, 137.42, 157.80, 158.01, 158.13, 158.46, 169.33, 172.67. HRMS (ESI): *m/z* calcd. for $C_{29}H_{41}N_4O_7$ $[M+H]^+$ 557.2970; found: 557.2985.

Compound 2a

Compound **1c** (1.75 g, 2.29 mmol) in DCM (80 mL) was slowly dropped into a solution of **1d** (1.70 g, 2.53 mmol) and DiPEA (1.31 g, 10.12 mmol) in DMF (15 mL) at −15°C. The solution was allowed to warm at room temperature and stirred overnight. The mixture was washed with brine, and then the aqueous phase was extracted with DCM three times. The combined organic phases were dried over $MgSO_4$. Purification by column chromatography with DCM/MeOH (40/1 then 30/1, v/v) afforded **2a** (2.50 g, 92%) as white foam.

^{1}H NMR ($CDCl_3$): δ = 1.30–1.80 (m, 33H, CH_2+CH_3), 3.10–3.11 (m, 8H, CH_2), 3.64 (s, 3H, CH_3), 4.05–4.62 (m, 4H, CH), 5.05–5.11 (m, 8H, CH_2), 5.28–5.59 (br, 4H, NH), 7.31–7.44 (m, 20H, CH). ^{13}C NMR ($CDCl_3$): δ = 22.56, 28.21, 28.50, 29.35, 31.36, 31.50, 31.81, 40.38, 40.67, 41.30, 52.16, 52.27, 52.48, 53.45, 66.48, 66.72, 80.30, 127.95, 128.18, 128.63, 128.66, 136.81, 156.89, 157.23, 171.70, 172.09, 172.74, 172.93, 173.14. HRMS (ESI): *m/z* calcd. for $C_{62}H_{84}N_8O_{15}Na$ $[M+Na]^+$ 1203.5948; found: 1203.5950.

Compound 2b

$LiOH·H_2O$ (0.36 g, 8.50 mmol) was added into a solution of **2a** (1.00 g, 0.85 mmol) in THF (15 mL), MeOH (20 mL), and

water (5 mL) at 0°C, and then the mixture was stirred for another 6 h at room temperature. After acidifying with 10% $KHSO_4$ to pH 3–4, the organic phase was extracted with DCM and washed with water, then dried over $MgSO_4$. Evaporation of all the solvents afforded **2b** (0.98 g, 99%) as white foam, which was used directly for next reaction.

^{1}H NMR (DMSO-d_6): δ = 1.16–1.37 (m, 25H, CH_2 + CH_3), 1.48–1.63 (m, 8H, CH_2), 2.96 (s, 8H, CH_2), 3.88 (s, 1H, CH), 4.11–4.26 (m, 3H, CH), 5.00–5.04 (m, 8H, CH_2), 6.81–6.90 (dd, 1H, NH), 7.19–7.24 (m, 4H, NH), 7.29–7.37 (m, 20H, CH), 7.77–7.86 (dd, 1H, NH), 7.89–7.98 (dd, 1H, NH), 8.03–8.12 (dd, 1H, NH). ^{13}C NMR (DMSO-d_6): δ = 22.84, 22.96, 23.10, 23.24, 28.61, 29.35, 29.55, 29.63, 30.99, 31.11, 31.89, 32.24, 40.18–40.70, 52.26, 52.44, 52.65, 54.85, 54.95, 65.58, 67.49, 78.58, 127.77, 128.18, 128.63, 128.80, 137.71, 155.81, 155.86, 156.52, 156.56, 171.83, 172.02, 172.08, 172.59, 173.93. HRMS (ESI): *m/z* calcd. for $C_{61}H_{83}N_8O_{15}Na$ $[M+H]^+$ 1167.5972; found: 1167.5929.

Compound 2c

EDC (0.54 g, 2.84 mmol) was added into a solution of **2b** (1.66 g, 1.42 mmol) and Np—OH (0.30 g, 2.13 mmol) in DCM (120 mL) at −10°C. After stirring overnight at room temperature, the mixture was washed with water and extracted with DCM three times. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was precipitated into hexane/ethyl acetate (1:2, v/v), and the solid was collected after filtration. Further drying of the solid *in vacuo* afforded **2c** (1.72 g, 94%) as a yellow foam, which was used directly for the next reaction.

HRMS (ESI): *m/z* calcd. for $C_{67}H_{86}N_9O_{17}$ $[M+H]^+$ 1288.6136; found: 1288.6126.

Compound 2d

TFA (2.30 g, 20.17 mmol) was added into a solution of **2a** (1.56 g, 1.32 mmol) in DCM (10 mL) at 0°C, and the mixture was stirred overnight at room temperature. Excess amount of MeOH was added to quench the reaction. Evaporation of solvents afforded **2d** as a slightly yellow foam (1.58 g, 100%).

^{1}H NMR (CD_3OD): δ = 1.39–1.50 (m, 16H, CH_2), 1.66–1.82 (m, 8H, CH_2), 3.10 (s, 8H, CH_2), 3.65–3.67 (m, 3H, CH_3), 3.85 (s, 1H, CH), 4.32–4.37 (m, 3H, CH), 5.04–5.10 (m, 8H, CH_2), 7.28–7.31 (m, 20H, CH). ^{13}C NMR (CD_3OD): δ = 21.93, 22.74, 29.21, 30.78, 31.00, 31.28, 39.99, 40.21, 51.47, 51.52, 52.31, 52.96, 53.20, 66.14, 127.50, 127.54, 127.73, 128.23, 137.14, 157.70, 172.93. HRMS (ESI): *m/z* calcd. for $C_{57}H_{77}N_8O_{13}$ $[M+H]^+$ 1081.5605; found: 1081.5614.

Compound 3a

Compound **2d** (0.73 g, 0.61 mmol) and DiPEA (0.53 g, 4.10 mmol) in DMF (3 mL) were added into a solution of **2c** (0.66 g, 0.51 mmol) in DCM (30 mL) at −15°C. The solution was allowed to warm at room temperature and stirred overnight. After washing with water, the organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was precipitated into hexane/ethyl acetate (1:1, v/v). After filtration, the solid was collected. Further purification of the crude product by column chromatography with DCM/MeOH (30:1 then 20:1, v/v) afforded **3a** as a colorless solid gel (0.97 g, 85%).

^{1}H NMR (DMSO-d_6): δ = 1.14–1.63 (m, 57H, CH_2 + CH_3), 2.96 (s, 16H, CH_2), 3.58 (s, 3H, CH_3), 3.89 (s, 1H, CH), 4.17–4.24 (m, 7H, CH), 5.00–5.05 (m, 16H, CH_2), 6.81–6.89 (m, 1H, NH), 7.19–7.21 (m, 8H, NH), 7.25–7.33 (m, 40H, CH), 7.79–8.22 (m, 7H, NH). ^{13}C NMR (DMSO-d_6): δ = 22.86, 23.02, 23.12, 23.26, 28.61, 29.15, 29.45, 30.82, 30.90, 31.91, 32.12, 32.31, 40.06–40.68, 52.19, 52.55, 52.82, 54.88, 65.59, 78.59, 127.76, 128.18, 128.62, 128.78, 130.11, 137.71, 155.79,155.89, 156.52, 171.72, 171.93, 172.02, 172.19, 172.26, 172.64, 172.87. HRMS (ESI): *m/z* calcd. for $C_{118}H_{156}N_{16}O_{27}Na$ $[M+Na]^+$ 2252.1224; found: 2252.7509.

Compound 3b

$LiOH{\cdot}H_2O$ (0.13 g, 3.09 mmol) was added into a solution of **3a** (0.69 g, 0.31 mmol) in THF (15 mL), MeOH (25 mL), and water (5 mL) at 0°C, and the mixture was stirred for another 8 h at room temperature. After acidifying with 10% $KHSO_4$ to pH 3–4, the organic phase was extracted with DCM and washed with water, then dried over $MgSO_4$. Evaporation of all the solvents afforded the product as white solid (0.68 g, 99%), which was used directly for next reaction.

^{1}H NMR (DMSO-d_6): δ = 1.14–1.63 (m, 57H, CH_2 + CH_3), 2.95–2.96 (m, 16H, CH_2), 3.89 (s, 1H, CH), 4.12–4.22 (m, 7H, CH), 4.99–5.04 (m, 16H, CH_2), 6.80–6.88 (m, 1H, NH), 7.18–7.23 (m, 8H, NH), 7.29–7.35 (m, 40H, CH), 7.77–8.13 (m, 7H, NH). ^{13}C NMR (DMSO-d_6): δ = 22.91, 22.99, 23.24, 28.60, 29.04, 29.18, 29.49, 29.55, 31.12, 32.08, 40.03–40.66, 52.88, 54.88, 65.59, 70.36, 78.60, 127.79, 128.18, 128.62, 128.78, 137.70, 156.52, 156.55, 172.03, 173.92. HRMS (ESI): *m/z* calcd. for $C_{117}H_{154}N_{16}O_{27}Na$ $[M+Na]^+$ 2238.1067; found:2239.2667.

Compound 3c

EDC (0.28 g, 1.47 mmol) was added dropwise to a mixture of **3b** (0.65 g, 0.29 mmol), HEMA (0.08 g, 0.59 mmol), and 4-*N, N*-dimethylaminopyridine (DMAP; 0.05 g) in dry DCM (100 mL) at 0°C. The mixture was stirred overnight at room temperature. After washing with water, the organic phase was dried over $MgSO_4$. Purification by column chromatography with DCM/MeOH (30/1 then 20:1, v/v) afforded the product as white solid (0.50 g, 74%).

^{1}H NMR (DMSO-d_6): δ = 1.24–1.63 (m, 57H, CH_2 + CH_3), 1.86 (s, 3H, CH_3), 2.96 (s, 16H, CH_2), 3.50–3.60 (m, 2H, CH_2), 3.89 (s, 1H, CH), 4.23–4.26 (m, 9H, CH + CH_2), 5.00–5.04 (m, 16H, CH_2), 5.67 (s, 1H, CH_2), 6.02 (s, 1H, CH_2), 6.83–6.89 (m, 1H, NH), 7.19–7.20 (m, 8H, NH), 7.29–7.41 (m, 40H, CH), 7.78–8.30 (m, 7H, NH). ^{13}C NMR (DMSO-d_6): δ = 18.36, 22.92, 23.28, 28.61, 29.56, 31.11, 31.91, 32.12, 32.25, 40.22–41.21, 52.16, 52.39, 52.90, 54.88, 54.95, 62.68, 62.79, 65.59, 70.36, 78.59, 126.62, 127.78, 128.18, 128.61, 128.78, 135.98, 137.71, 155.89, 156.52, 166.78, 171.94, 172.04, 172.30, 172.66, 172.86. HRMS (ESI): *m/z* calcd. for $C_{123}H_{162}N_{16}O_{29}Na$ $[M+Na]^+$ 2350.1591; found: 2351.3609.

Compound 3d

Compound **3a** (70.00 mg, 0.03 mmol) was dissolved in TFA (2 mL), and then HBr (33% in acetic acid; 148.00 mg, 0.6

mmol) was added. After stirring for 1 h, the mixture was precipitated into ethyl ether, which was then collected by ultracentrifugation. The product was dissolved in water and freeze dried under high vacuum to afford **3d** as slightly yellow foam (60 mg, 93%).

^{1}H NMR (D_2O): δ = 1.36–1.37 (m, 16H, CH_2), 1.59–1.85 (m, 32H, CH_2), 2.91–2.92 (m, 16H, CH_2), 3.64–3.65 (m, 3H, CH_3), 3.98–4.01 (m, 1H, CH), 4.19–4.32 (m, 7H, CH).

PLLy(Z)

Monomer **3c** (0.37 g, 0.16 mmol) and AIBN (1.8 mg, 0.5 wt % to the monomer) were dissolved in DMF (0.4 mL) in a Schlenk tube. The solution was thoroughly deoxygenated by several freeze-pump-thaw cycles and then stirred at 65°C for 24 h. After cooling to room temperature, the mixture was precipitated into ethyl acetate. After ultracentrifugation, the polymer was collected. Further drying under vacuum afforded white solid (210 mg, 57%).

^{1}H NMR (DMSO-d_6): δ = 1.24–1.61 (m, 57H, CH_2 + CH_3), 2.94 (s, 16H, CH_2), 3.88–4.22 (m, 12H, CH + CH_2), 4.98–4.99 (m, 16H, CH_2), 6.88 (br, 1H, NH), 7.19–7.21 (m, 8H, NH), 7.31–7.33 (m, 40H, CH), 7.78–8.01 (m, 7H, NH). ^{13}C NMR (DMSO-d_6): δ = 22.99, 23.24, 28.60, 29.55, 32.14, 39.46, 40.22–40.67, 52.93, 54.96, 65.59, 78.58, 127.76, 128.16, 128.75, 128.78, 137.69, 155.88, 156.51, 171.93, 172.01, 172.64. Some signals from the backbone were not resolved.

PLLy

Polymer PLLy(*Z*) (0.03 g, 0.013 mmol) was dissolved in TFA (1.5 mL), and then HBr (33% in acetic acid; 16.00 mg, 0.065 mmol) was added. After stirring for 1 h, the mixture was precipitated into ethyl ether, which was then collected by ultracentrifugation. The product was dissolved in water and freeze dried under high vacuum to afford PLLy (23 mg, 95%).

^{1}H NMR (DMSO-d_6): δ = 1.24–1.66 (m, 53H, CH_2 + CH_3), 2.78 (s, 16H, CH_2), 3.91–4.27 (m, 12H, CH + CH_2), 7.44–8.63 (m, 34H, NH + NH_3^+). ^{13}C NMR (DMSO-d_6): δ = 21.53, 22.72, 26.76, 26.93, 29.58, 30.92, 31.80, 40.23–40.57, 52.76, 54.96, 168.85, 171.98. Some signals from the backbone were not resolved.

ACKNOWLEDGMENTS

The authors thank Dr. Hongmei Deng from the Instrumental Analysis of Research Center (Shanghai University) for her assistance in NMR measurements. This work is financially supported by the National Natural Science Foundation of China (Nos.: 21034004, 21104043, and 20974020) and by the Science and Technology Commission of Shanghai (Nos.: 10520500300 and 11PJ1404100).

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