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Supramolecular Polymers

pH-Regulated Selectivity in Supramolecular Polymerizations: Switching between Co- and Homopolymers

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Abstract: A strategy is presented to regulate the selectivity in aqueous supramolecular polymerizations by changes in pH. In neutral buffered conditions, oppositely charged phenylalanine-based dendritic peptide amphiphiles self-assemble into $(A–B)_n$ alternating copolymers of low polydispersity when mixed in a 1:1 comonomer feed ratio. Via pH switch of the glutamic acid and lysine side chains, attractive Coulomb interactions in the coassembled materials are screened and selective polymerization occurs to form $(A)_n$ homopolymers of the acidic comonomer at low pH and $(B)_n$ homopolymers of the basic comonomer at high pH, while the complementary comonomer is released during the transition. Reversible switching is demonstrated between these three different polymeric states, which were characterized by CD and fluorescence spectroscopy, using a peptide based minimalistic fluorophore/quencher pair, and transmission electron microscopy.

Introduction

Proteins and nucleic acids are two classes of key polymeric biomolecules that are produced by living organisms. In the case of proteins, their specific amino acid sequence is encoded to guide their folding into a variety of functional biopolymers. This precisely defined arrangement of monomeric building blocks into complex 3D assemblies has inspired chemists to investigate synthetic polymerizations of controlled monomer sequences.[1] Most approaches are kinetically controlled,[1b,2] use template approaches,[3] and chain-shuttling mechanisms to yield periodic patterns,[4] or block copolymer architectures.[5] Compared to covalent polymer synthesis,[1] there are few examples that enable control over sequence specificity, monomer incorporation, or block polymer morphologies by using supramolecular chemistry:[6] Winnik, Manners, and co-workers pioneered kinetic control in the self-assembly of block copolymers with crystallizable cores yielding fiber-like micelles with tunable length, multiblock structure, and very low polydispersity;[7] Sijbesma and co-workers reported self-sorting in bisurea-based rod-like micelles in water, whereby a mixture of different monomers selectively assemble into homopolymeric rod-like aggregates.[8] To our knowledge, no attempts have been made to design a covalent or supramolecular polymerization strategy, whereby the polymer composition can be switched reversibly between two or more states by an external trigger.[9]

In a complementary approach to the self-assembly of pH-switchable small zwitterions,[10] or coiled-coil peptide motifs that are stabilized by electrostatic interactions,[11] and the larger body of work on β-sheet encoded peptides,[12] we recently reported ampholytic supramolecular copolymers.[13] In these self-assembled rod-like materials, complementary sites of interaction (i.e., pairs of acid/base groups) are embedded into the pentapeptide-sequenced dendritic comonomers via alternating hydrophobic/hydrophilic amino acids. Based on this design principle, we hereby demonstrate an approach to regulate the selectivity in supramolecular polymerizations by pH. In neutral buffer, phenylalanine–lysine (FK)- and phenylalanine–glutamic acid (FE)-based dendritic amphiphilic peptides **1** and **2** self-assemble into well-defined **1**–**2** copolymers (Figure 1). By switching off the negative or positive charges on the oppositely charged comonomers by modulation of the pH,[14] selective homopolymerization occurs with the simultaneous release of the complementary comonomer. This is the first report of a supramolecular polymerization in solution that can be switched reversibly between three different composition states: homopolymers of **1**, **1**–**2** copolymers, and homopolymers of **2**.

Results and Discussion

Using a convergent synthetic approach, we incorporated very hydrophobic FE- and FK-based alternating amino acid sequences in each of side arms of the C_3-symmetrical comonomers **1** and **2**, as well as an apolar hexyl spacer coupled to a hydrophilic tetraethylene glycol peripheral dendron (Figure 1). The latter considerably improved the solubility of the building

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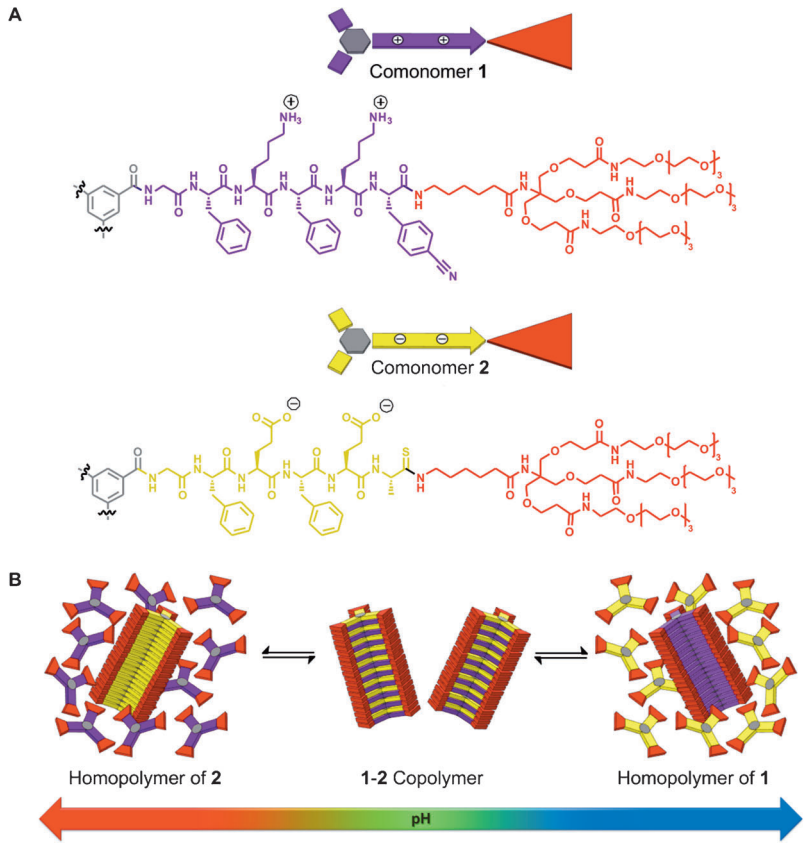

Figure 1. A) Chemical structures of the C_3-symmetric dendritic peptide comonomers **1** and **2**; B) their pH-regulated supramolecular polymerization into homopolymers of **1** and **2**, at high and low pH respectively, and **1**–**2** copolymers at neutral pH.

blocks. Finally, we also incorporated the fluorophore *p*-cyanophenylalanine (Cnf) and the thioamide analogue of alanine (Ala') on the FK- and FE-based comonomers, respectively. The aim was to investigate the supramolecular polymerization by fluorescence spectroscopy and resonance energy transfer (RET), a powerful tool to study distance-dependent events, such as conformational changes in proteins. The Cnf–thioamide couple was coined as a minimalistic fluorophore/quencher pair by Petersson and co-workers and has a working distance of 0.8–3.0 nm, which is well-suited for our copolymers.[15]

Photoluminescence spectroscopy experiments containing only the fluorescent monomer **1** show a sharp 50% decrease in the emission intensity at pH > 9.5 (Figure 2A and Figure S1 in the Supporting Information). This is a first indication that, due to the deprotonation of the lysine side chains, the core of the dendritic peptide becomes more hydrophobic and self-assembly into homopolymers occurs, which quenches the fluorescence of the Cnf moiety. In addition, the presence of free amines has been reported to quench the Cnf emission.[16] If, at neutral pH, the complementary comonomer **2** is added in a 1:1 feed ratio to a solution of **1**, the fluorescence intensity drops by 35% (Figure 2A and Figure S2 in the Supporting Information). This is strong evidence that supramolecular **1**–**2** copolymers are formed, which leads to a RET-promoted decrease in the observed fluorescence intensity. If the pH of the 1:1 mixture of **1** and **2** is decreased to pH < 4, the emission band increases to the intensity of the isolated solution of **1**. Due to protonation of the glutamic acid based monomer, the **1**–**2** copolymer falls apart because of a loss of the attractive Coulomb interactions in the oppositely charged side chains. Monomer **1** is thereby released and its photoluminescent properties restored. Intriguingly, by raising the pH of a coassembled material of **1** and **2** from pH 7.4 to pH > 10, the emission drops by a further 20% to about the same value observed in the isolated solution of **1** (Figure 2A and Figure S2 in the Supporting Information). The homopolymerization of the free amine derivative of **1** is thereby not influenced by the presence of **2** in solution. Remarkably, the three different polymeric states can be reversibly switched by repeated pH cycling (Figure 2B and Figure S3 in the Supporting Information). We postulate the different states to be homopolymers of **1** (pH > 10), copolymers of **1**–**2** (neutral pH), and homopolymers of **2** (pH < 4).

To correlate the spectroscopic findings with morphological investigations, negative-stain transmission electron microscopy (TEM) experiments were performed. After depositing a solution of either comonomer at pH 7.4, small isotropic objects of 9 nm for solutions of **1** (see the Supporting Information, Figure S4A, B) and 7 nm for solutions of **2** (see the Supporting Information, Figure S6A, B) were obtained. This confirms that, at neutral pH, the 6 cationic charges in monomer **1** and 6 anionic charges in monomer **2** prevent the formation of supramolecular homopolymers due to electrostatic repulsive interactions.

However, by raising the pH of the solution containing the basic monomer **1** to pH 11, anisotropic nanorod-like structures were obtained with a number-average length $L_n = 38$ nm and a thickness of 11 nm (see the Supporting Information, Figures S4C, D and S5). The thickness of the rods is in good agreement with the diameter of the molecular building blocks, which corresponds to an estimated 7.2 nm for the extended hydrophobic core and 12.5 nm including the stretched out hydrophilic dendron. In contrast, decreasing the pH of a solution of the acidic monomer **2** led to very long rods with an absolute length that could not be determined accurately (> 1 μm; see the Supporting Information, Figure S6C, D). Remarkably, we were able to resolve a left-handed helical secondary structure in these rods, which show thicknesses ranging from 6.9 nm to

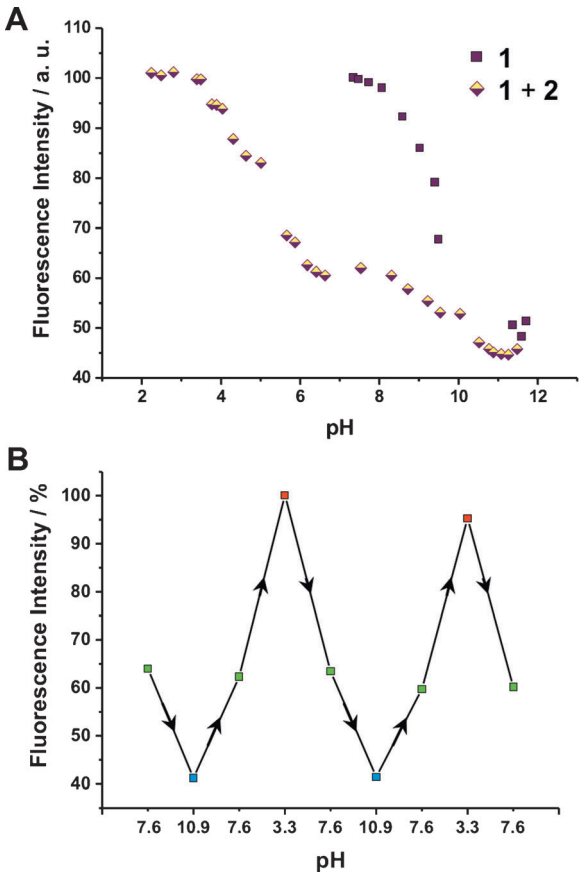

Figure 2. A) pH-dependent fluorescence emission intensity (λ_{em} = 295 nm, λ_{exc} = 240 nm) of the fluorescent monomer **1** alone (6 μM, shown as purple squares), and a 1:1 mixture of **1** (6 μM) and the quenching monomer **2** (6 μM) in 5 mM phosphate buffer (shown as purple/yellow diamonds); B) pH-dependent fluorescence intensity after repeated addition of NaOH and HCl.

10.4 nm depending on their orientation in the field of view (see the Supporting Information, Figures S7, S8, and S11 A).

Crucially, when both comonomers were premixed in a 1:1 ratio at pH 7.4, well-defined anisotropic structures exhibiting right-handed helical arrangement were observed with a number average rod-length L_n = 56 nm and a polydispersity index (PDI) L_w/L_n = 1.3 (Figure 3, 4B, S9A–B and S11B).[7] Their thicknesses ranged from 6.4 nm to 10.4 nm (see the Supporting Information, Figure S10), and were in good agreement with the diameter of the molecular building blocks. The polydispersity for the contour length distribution of the rod-like copolymers was very narrow. While this could not be directly compared to the molecular weight distribution of supramolecular polymers, it is known that such a narrow distribution can only be obtained in a non-cooperative process. The copoly-

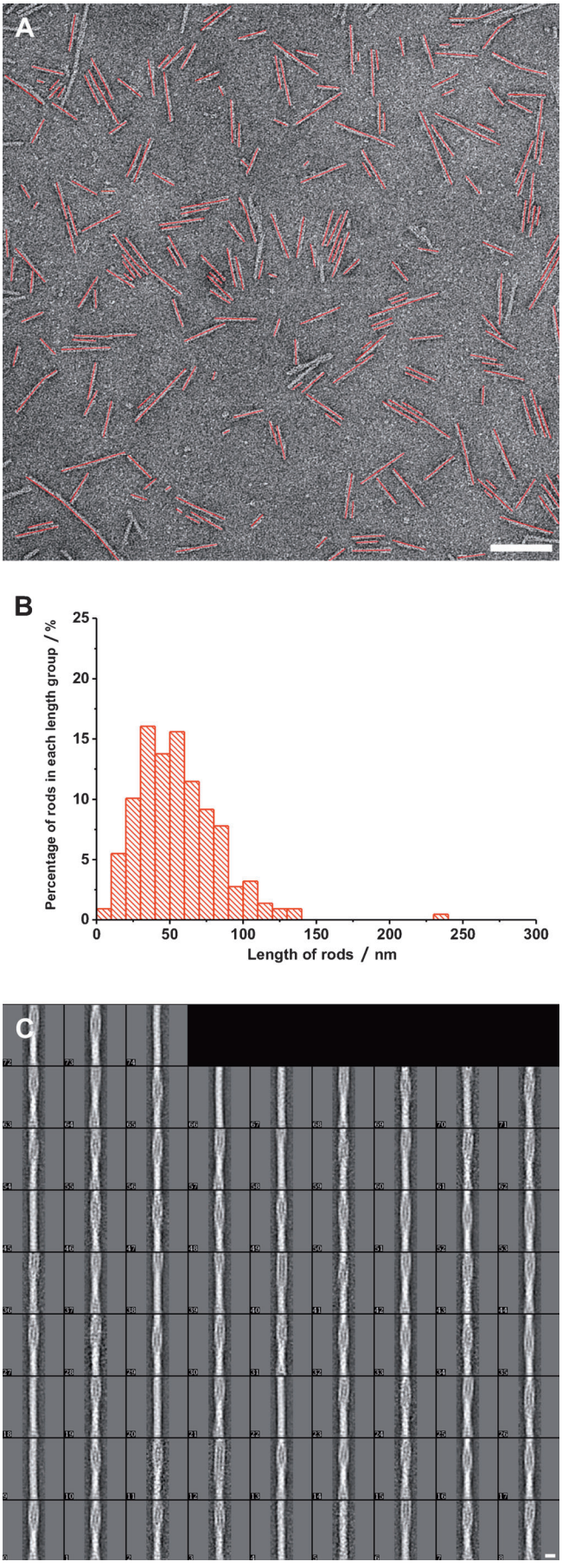

Figure 3. A) TEM image of the copolymer of **1** and **2** at pH 7.4; individual copolymers measured for length histogram are marked with red lines (scale bar = 100 nm); B) length histogram of the rod-like copolymer: L_n = 56 nm, L_w = 70 nm, σ = 28 nm, L_w/L_n = 1.3, σ/L_n = 0.5, n = 218. (Values of L_n and L_w were calculated as previously reported[7]); C) all class averages of the copolymer of **1** and **2** at pH 7.4 (scale bar = 10 nm).

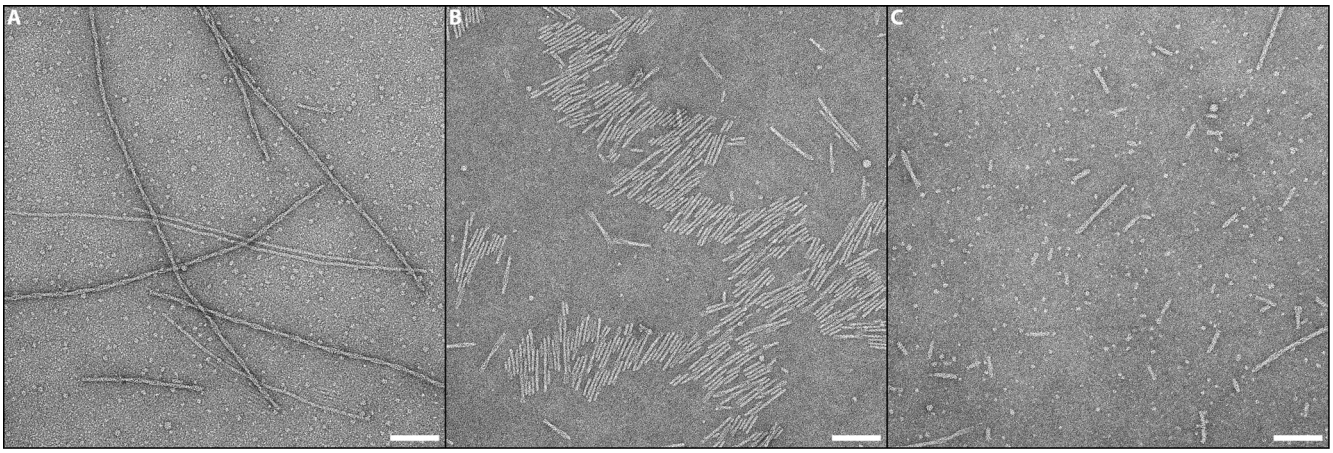

Figure 4. TEM images: A) The homopolymer of **2**—monomer **1** mixture at pH 2.0; B) the **1**–**2** copolymer at pH 7.4; C) the homopolymer of **1**—monomer **2** mixture at pH 11.0 (scale bars = 100 nm).

mers therefore behaved like step-growth polymers.[6] Van der Schoot and Jabbari-Farouji recently disclosed a theoretical model for supramolecular copolymerizations in two-component systems.[17] In line with their predictions for a non-cooperative mechanism based on two comonomers that have no driving force for homopolymerization, we postulate that the copolymers have a strictly alternating **1**–**2** monomer sequence in the copolymers.

After acidifying a solution of the copolymers to pH 2, we observed homopolymers of **2** as micrometer long nanorods and monomers of **1** as <10 nm-sized spherical objects (Figure 4A and Figure S9C,D in the Supporting Information). When the pH was increased from pH 7.4 to pH 11, homopolymers of **1** were obtained as short nanorods in the presence of monomers of **2** as nanosized spheres (Figure 4C and Figure S9E,F in the Supporting Information). Together with the photoluminescence studies, these findings confirm that, under neutral conditions, supramolecular polymerization into well-defined copolymers of **1** and **2** occurs. Note the elegance of our approach; repulsive Coulomb interactions between monomers of the same charge prevent their assembly into homopolymers. However, attractive Coulomb interactions in the oppositely charged comonomers reinforce self-assembly of β-sheet encoded peptide sequences.[13] Through pH switching of the basic and acidic peptide monomers, attractive electrostatic interactions in the copolymers are screened, and selective homopolymerization of **1** (high pH) or **2** (low pH) occurs due to the hydrophobic phenylalanine based core, while the complementary comonomer is released.

To further elucidate the pH-regulated self-assembly into homo- and hetero-copolymers of **1** and **2**, we performed circular dichroism (CD) spectroscopy experiments. Upon changing the pH from pH 7.4 to pH 12.0 for **1** and from pH 7.4 to pH 3.2 for **2**, significant changes in the CD bands were observed (see the Supporting Information, Figure S12–S14). Consistent with the results obtained from TEM experiments, we assign these changes to a pH-induced monomer to homopolymer transition. For the acidic FE-based building block, the sharp transition occurred at pH 3.8 (see the Supporting Information, Figure S14), whereas for the basic FK-based monomer, the transition occurred at pH 10.5 (see the Supporting Information, Figure S13). Both values are in good agreement with their expected pK_a values. The CD spectrum obtained upon mixing an equimolar solution of **1** and **2** at neutral pH deviates strongly from the linear combination of the two isolated solutions of both comonomers at the same pH (see the Supporting Information, Figure S12D). If the pH of the same solution of the **1**–**2** hetero-copolymers is adjusted to either pH 12 or pH 2, the CD spectra obtained are identical to the linear combination of the measured solutions for the homopolymer of **2** and monomer **1**, or homopolymer of **1** and monomer **2** (see the Supporting Information, Figure S12C,E). This is in full agreement with the interpretation of fluorescence spectroscopic data and TEM micrographs. When switching off the copolymerization of **1** and **2** at high and low pH, we follow the characteristic CD signals for the copolymers; the sharp transitions at pH 3.8 and pH 10.5 overlap with the monomer-homopolymer transitions observed for the isolated solutions of **1** and **2** (Figure 5A and Figures S15 and S16 in the Supporting Information). Upon pH switching, the **1**–**2** copolymers fall apart, and self-assembly into the respective homopolymers takes place while the complementary comonomer is released from the copolymers.

To utilize the concept of pH-regulated selectivity in supramolecular polymerizations, it would be advantageous if the incorporated switches could also be adjusted for a particular application. For example, tuning instabilities towards pH and ionic strength is a highly effective strategy for synthetic gene delivery vectors, whereby a decrease in pH and osmotic swelling triggers the release of genome material from intracellular compartments.[18] With this in mind, we investigated the ionic-strength-dependent copolymer-to-homopolymer transitions; in the presence of 25 mM NaCl, the pH stability window for the supramolecular copolymerization narrowed from pH 3.8–pH 10.5 to pH 4.2–9.5 (Figure 5B and Figures S17 and S18 in the Supporting Information). As expected, an increase in the ionic strength screened the attractive Coulomb interactions

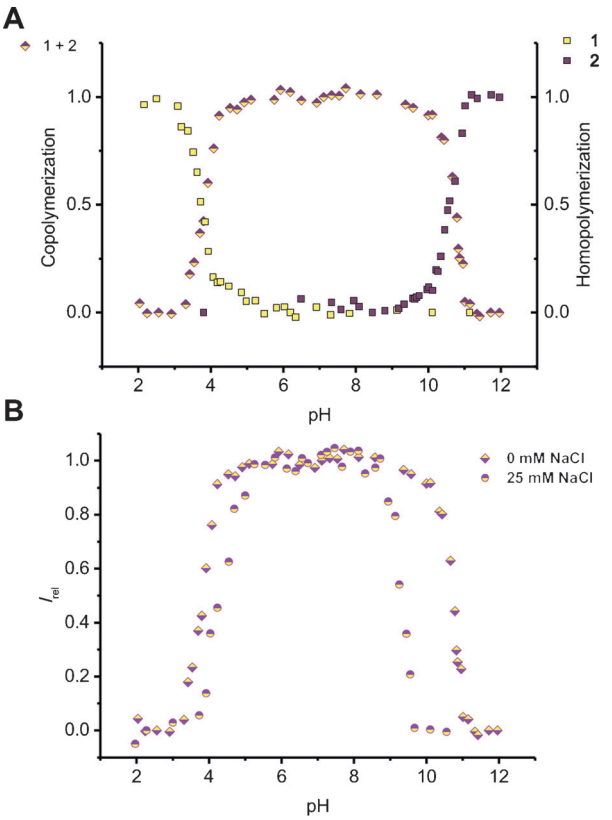

Figure 5. A) Normalized CD data for titrations of a 60 μM aqueous solution containing a 1:1 mixture of comonomers **1** and **2** (mixed-colored data points, left *y* axis), and the isolated mixtures of the monomers (single-colored data points, right *y* axis); $I_{rel}=1$ is set for the polymerized state as switched 'on' and $I_{rel}=0$ is set for the polymerized state as switched 'off' (see the Supporting Information, Figures S17–S20); B) normalized CD data for titrations of a 60 μM aqueous solution containing a 1:1 mixture of comonomers **1** and **2** at different pH values in phosphate-buffered (5 mM) water, without NaCl, and with 25 mM added NaCl (based on Figures S17–S20); $I_{rel}=1$ is set for the copolymerized state as switched 'on' and $I_{rel}=0$ is set for the copolymerized state as switched 'off'.'

between oppositely charged monomers and destabilized the **1**–**2** copolymers. In contrast, under neutral conditions (pH 7.4), full disassembly of the copolymers occurred only at a critical concentration of 200 mM NaCl (see the Supporting Information, Figures S19–S21). Furthermore, in contrast to the large majority of reported supramolecular polymers that are enthalpy driven,[6] we observed that the **1**–**2** copolymers could not be depolymerized simply by increasing the temperature (see the Supporting Information, Figure S22), suggesting that desolvation and entropic effects are very pronounced.

Conclusions

In conclusion, we have presented a biomimetic strategy to regulate the selectivity in supramolecular polymerizations by modulation of the pH. Attractive Coulomb interactions in oppositely charged dendritic peptide amphiphiles reinforced weak noncovalent interactions to form alternating supramolecular copolymers. Upon pH switching of the lysine and glutamic acid peptidic monomers, attractive electrostatic interactions in the coassembled materials were lost, and selective polymerization occurred to form homopolymers of the basic comonomer at high pH and homopolymers of the acidic comonomer at low pH. The transition between the copolymers and either of the homopolymers narrowed on increasing the ionic strength. The general nature of the concept could be readily utilized to fabricate new biomaterials in solution, in the gel state, or on surfaces.

Experimental Section

The detailed synthetic procedures, material characterization, and full details about the instrumentation can be found in the Supporting Information. Fluorescence spectra were recorded on a FP-6500 (JASCO) using the software Spectra Manager 2.08.04 and processed with Origin Pro 9.1 G. All spectra were recorded at 25 °C with monomer concentrations of 6 μM, each in 5 mM phosphate buffer. The pH values were adjusted by the addition of aqueous HCl or NaOH. For all experiments, the excitation wavelength was 240 nm and emission data was collected from 260 nm to 380 nm using quartz fluorometer cells with a path length of 1 cm. The excitation bandwidth was 3 nm and the emission bandwidth was 5 nm, the scan rate was 500 nm min^{-1}, and the data interval was 0.1 nm. CD spectra were recorded on a J-815 (JASCO) using the software Spectra Manager 2.08.04 and processed with Origin Pro 9.1 G. All spectra were recorded at 20 °C with a total monomer concentrations of 60 μM in 5 mM phosphate buffer using quartz cells with a path length of 2 mm. The low monomer concentrations made sure that the HT signal was lower than 600 V at all times. In the UV/Vis spectra, no evidence for scattering was observed in any of the solutions. The pH values were adjusted by addition of aqueous HCl and NaOH. All Spectra were corrected by subtraction of the background (buffer). The associated UV/Vis spectra were recorded on a U-650 (JASCO), using the software Spectra Manager 2.08.04, directly after the fluorescence measurement. The data was processed with Origin Pro 9.1 G. The UV/Vis spectra were collected between 200 nm and 320 nm. The procedure for grid preparation and image recording for negative-stain EM was as follows: In brief, 4 μL sample droplets were adsorbed for 1 min on freshly glow-discharged copper grids (Agar scientific; G2400C) covered by a thin, continuous carbon film. The grids were then negatively stained with 0.75% uranyl formate (Polysciences) for 1 min before blotting with filter papers (Whatman no. 4).[19] All images were recorded with a JEOL JEM-1400 electron microscope equipped with a LaB_6 cathode and operated at 120 kV. Digital electron micrographs were recorded with a 4k×4k CMOS camera F416 (TVIPS) under minimal dose conditions (15–20 electrons/Å^2) at a calibrated magnification of 67,535×, resulting a pixel size of 2.32 Å. The lengths of individual rod-like filaments were measured using boxer from EMAN software package.[20] The histograms were prepared using StatPlus:mac LE (AnalystSoft) with Excel 2011 (Microsoft).

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Keywords: controlled polymerization · self-assembly · pH regulation · polymers · supramolecular chemistry

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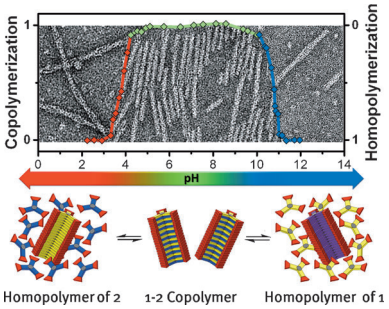
FULL PAPER

Switchcraft: A strategy to regulate the selectivity in aqueous supramolecular polymerizations is presented. In neutral buffer, oppositely charged dendritic peptide amphiphiles selectively self-assemble into alternating copolymers. At high and low pH, the formation of either the basic or acidic homopolymer occurs while the complementary co-monomer is released. The transition between these three different polymeric states is fully reversible and can be switched multiple times.



Supramolecular Polymers

*H. Frisch, Y. Nie, S. Raunser, P. Besenius**

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pH-Regulated Selectivity in Supramolecular Polymerizations: Switching between Co- and Homopolymers