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Tuning the pH-triggered self-assembly of dendritic peptide amphiphiles using fluorinated side chains

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We report the synthesis of a series of anionic dendritic peptide amphiphiles of increasing hydrophobic character. By establishing state diagrams we describe their pH and ionic strength triggered self-assembly into supramolecular nanorods in water and highlight the impact of hydrophobic shielding in the supramolecular polymerisation process. Via the incorporation of fluorinated peptide side chains the pH-triggered monomer to polymer transition at physiological ionic strength is shifted from pH 5.0 to pH 7.4. We thereby show that by compensating attractive non-covalent interactions and hydrophobic effects with repulsive electrostatic forces, a concept we refer to as frustrated growth, is a sensitive tool in order to manipulate one-dimensional supramolecular polymerisation processes in water.
We are particularly interested in well-defined and stimuli-responsive nanomaterials that are designed to undergo morphological transitions triggered by specific changes in a physiological environment. These hold much promise for applications in biomedical imaging and therapy. We are planning to develop methodologies whereby the acidity in the microenvironment of a tumour interior or inflamed tissue induces the triggered self-assembly of small molecules into larger nanorods. The additional benefit of fluorinated building blocks is their potential use in 19F-MRI, which would allow to quantify the selective tumour retention and accumulation in cancer diagnosis and therapy.

Results and discussion

Synthetic routes

The synthesis of the dendritic peptide amphiphiles 6 and 12 followed a convergent approach (Scheme 1A; full details can be found in the ESI). First, the Cbz-protected tri-L-phenylalanine 2 was synthesized using conventional solid-phase peptide synthesis (SPPS). Using standard peptide coupling reagents, the tert-butyl protected Newkome dendron 1, or 6-aminohexanoic acid extended dendron 8 were coupled to 2 in order to obtain the Cbz-protected dendronised triphenylalanines 3 and 9. After hydrogenation using Pd/C as catalyst the amine derivatives 4 and 10 were coupled to 1,3,5-benzentricarbonyl trichloride to obtain the branched self-assembly units 5 and 11. Finally after acidic deprotection of 5 and 11, the dendritic nonaphenylalanine peptide amphiphile 6 was obtained after four steps in a moderate non-optimised overall yield of 13%, and 12 after four steps in a non-optimised overall yield of 22% (Scheme 1A). In 6 the hydrophobic core and hydrophilic dendron are directly connected, while 12 contains an apolar hexyl linker between the same dendritic nonaphenylalanine core and the peripheral carboxylic acid Newkome dendron.

In order to create a dendritic core that is more hydrophobic than the one in 12, we incorporated a L-phenylalanine-di-(O-allyl-L-tyrosine) into the same convergent synthesis as described before (Scheme 1B) including an apolar hexyl linker between the dendritic nonpeptide core and the peripheral carboxylic acid Newkome dendron. The allyl ether functional groups are very useful since they can easily be modified via thiol-ene type click chemistry, using 2,2,2-trifluoroethanethiol to incorporate fluorinated side chains into the hydrophobic peptide block. Note that we had to install a phenylalanine amino acid on the N-terminus rather than a protected tyrosine, since we encountered very low yields when coupling tri-(O-allyl-L-tyrosine) derivatives to the benzentricarbonyl trichloride core, most likely due to steric issues. Using conventional Fmoc-SPPS chemistry we prepared Fmoc-phenylalanine-di-(O-allyl-L-tyrosine). In four similar steps as described for compound 12 the amphiphiles 17 was successfully obtained. After UV-
initiated thiol-ene click chemistry using 2,2-dimethoxy-2-phenylacetophenone (DMPA) in a THF/water mixture 1:1 we isolated the target fluorinated dendritic peptide amphiphile 18, after five steps in a non-optimised overall yield of 6% (Scheme 1B).

Spectroscopic investigations into the pH and ionic strength triggered self-assembly

The dendritic peptide amphiphiles 6, 12 and 18 equipped with nine carboxylic acids groups turned out to be highly soluble in aqueous buffers.

First, we investigated the self-assembly of dendritic peptide amphiphile 6 in phosphate buffer using circular dichroism (CD) spectroscopy. At pH 9.0 in 10 mM phosphate buffer, the CD spectra suggest that no aggregation takes place (Fig. 2A and S1). This agrees with observations we have made before,\(^\text{45}\) in slightly basic pH and at low ionic strength repulsive Coulombic interactions from the charged dendritic carboxylate groups in the hydrophilic shell of the peptides prevent supramolecular polymerisation into large macromolecular structures. Surprisingly we were not able to screen these charge-charge repulsive interactions by increasing the ionic strength up to 1 M NaCl at pH 9.0 (Fig. 2A) or by acidifying the buffer to pH 6 (Fig. 2B). Since the CD spectra are identical in pH 9.0, 7.4 and 6.0, both at low and high ionic strength (Fig. S1) it thereby becomes apparent that an apolar spacer between the hydrogen bonding hydrophobic core and hydrophilic shell is critical for self-assembly.

This was verified by investigating the supramolecular polymerisation of the dendritic peptide amphiphile 12 in full detail. At neutral pH 7.4, in 10 mM phosphate buffer and 0 M NaCl, a CD spectrum with at weak negative band at 210 nm is observed, that is very similar to the one obtained for compound 6 (Fig. 3 and S2). At pH 7.4, the addition of NaCl leads the appearance of a positive band at \(\lambda = 203\) nm, to a shift of the negative band from \(\lambda = 210\) nm to 220 nm and a significant increase in the intensity. This is a good indication for the self-assembly into ordered chiral supramolecular polymers. By electrostatic screening of the negative charges in the periphery of the supramolecular nanorods, the polymerisation becomes more favourable.\(^\text{45, 52}\) Similarly after lowering the pH from 7.4 to pH 5.0 the same transitions in the CD spectra are observed, which indicates the formation of supramolecular polymers. These findings suggest that at physiological pH the self-assembly of the polyamionic dendritic peptide 12 is dictated by a mechanism of frustrated growth: attractive supramolecular interactions, hydrogen-bonding and hydrophobic effects, that drive the monomers to polymerise are opposed by repulsive Coulomb interactions which disfavour self-assembly.\(^\text{35, 37, 39, 43, 52}\)

The multistimuli-responsive self-assembly of these peptidic supramolecular polymers can be most conveniently visualised in an ionic strength and a pH dependent contour plot, which we refer to as state diagram\(^\text{4}\) (Fig. 3D). It can clearly be observed that at 100 mM NaCl the transition from a disassembled state at pH 7.4 to a fully polymerised state at pH 5.0 is much sharper than the transition at pH 7.4, from 0 to 1 M NaCl. Screening of the repulsive interactions by protonation of the dendritic carboxylic acids occurs at a pH value between pH 5.0 and pH 6.0, which is at least one unit higher than expected for a common organic carboxylic acid in water. The \(pK_a\) for a Newkome-type dendritic carboxylic acid was reported to be about 4.\(^\text{51}\) We have previously observed a similar shift in the apparent \(pK_a\) value for amphiphilic dendritic carboxylic acids which we attributed due to be driven by the aggregation process,\(^\text{43}\) this is a well-known phenomenon for polymeric weak acids and self-assembled fatty acids.\(^\text{52-54}\)

Finally we investigated the self-assembly of the most hydrophobic compound out of the small series of dendritic peptide amphiphiles 6, 12 and 18. CD bands for compound 18 become red-shifted compared to 6 and 12, due to the presence of the functionalised O-allyl-tyrosine side chains (Fig. 4 and be S3). At pH 9.0 and 0 M NaCl we expect the carboxylic acids to fully deprotonated and the dendritic amphiphiles to be molecularly dissolved. The CD spectra reveal a negative band.
at $\lambda = 210$ nm and a positive band at $\lambda = 225$ nm. Upon lowering the pH from pH 9.0 to pH 7.4, pH 6.0 and pH 5.0, or by increasing the ionic strength, the observed bands shift significantly: a strong positive band at $\lambda = 205$ nm appears, the negative band shifts from $\lambda = 210$ nm to $\lambda = 220$ nm, and the positive one from $\lambda = 225$ nm to $\lambda = 230$ nm. Both CD bands increase in intensity, while another additional weakly negative band at $\lambda = 245$ nm appears. The pH and ionic strength dependent contour plot shows that the supramolecular polymerisation for the fluorinated monomer is clearly shifted towards higher pH values and lower ionic strength compared to dendritic peptide amphiphile 12 (Fig. 3D and Fig. 4D). The pH-triggered monomer to polymer transition at physiological ionic strength is shifted from pH 5.0 (for monomer 12) to pH 7.4 (for monomer 18). The state diagram thereby highlights the importance of hydrophobic effects in the self-assembly of amphiphilic dendritic carboxylic acids. The previously discussed apparent $pK_a$ shifts (the intrinsic $pK_a$ of the dendritic carboxylic acid is about 4) are increased by another two units in the case of monomer 18 compared to 12: due to the higher thermodynamic driving force for supramolecular polymerisation the carboxylic acids in the hydrophilic shell become weaker. These findings are in good agreement with $pK_a$ shifts observed in the self-assembly of linear peptide amphiphiles: the Goldberger lab has reported amphiphiles based on a palmitic acid tail coupled to a XAAAEEE oligopeptide. Due to the electrostatic repulsion of the deprotonated glutamic acids (E) at neutral pH, these molecules are present as isolated monomers at low concentration. By acidifying the solution self-assembly into nanofibers occurs, driven by the formation of intermolecular $\beta$-sheets. The balance of repulsive to attractive interactions can be manipulated by varying the hydrophobic amino acid (X) embedded in the $\beta$-sheet forming region: if the driving force for $\beta$-sheet formation in the olioalanine block XAAA is enhanced via the incorporation of a more hydrophobic amino acid (tryptophan (Y), valine (V), phenylalanine (F), or isoleucine (I)), the propensity for $\beta$-sheet formation follows the trend $I > F > V > Y$, the triggered self-assembly is shifted from pH 6.0 to pH 6.6; the apparent $pK_a$ of the oligoglutamic acid EEEE block is therefore shifted from their intrinsic $pK_a$ of 4.7-4.9 by up to two units.
Similarly, weakening of the basic character of protonated lysine and histidine side chains (apparent pK_a of 7 and 4.5 respectively), as well as a weakening of the acidic character of aspartic acid side chains (apparent pK_a of 6) has been observed by Matile and coworkers in the β-sheet directed self-assembly of p-octyphenyl β-barrel pores embedded in lipid bilayers. Due to the spacial proximity and electrostatic repulsion of the multiply charged bases or acids in these synthetic pores, the intrinsic pK_a of the base/acid is shifted, an observation which was summarized in the intermediate internal charge repulsion (ICR) model. Indeed, the delicate balance of attractive and repulsive features in these barrel-stave supramolecules is not too dissimilar to the frustrated assembly term we have used to describe the supramolecular 1D nanorod formation: lack of ICR has been thought to account for ‘implosion’, low ICR for contraction, high ICR for expansion, and excess ICR for ‘explosion’ of the β-barrels. Furthermore contributions of the surrounding bilayer have to be taken into account: the external membrane pressure (EMP) model is supposed to protect the overcharged barrels from exploding and to promote the implosion of undercharged barrels. This effect has important consequences for the catalytic activity of the synthetic pores.

In summary, we have been able to build state diagrams, which are well known for self-assembled natural spherical or filamentous viruses, in order to investigate pH and ionic strength dependent self-assembly of dendritic peptide amphiphiles into supramolecular polymers in water. We have highlighted the impact of hydrophobic shielding in the supramolecular polymerisation process: via the incorporation of fluorinated peptide side chains the pH-triggered monomer to polymer transition at physiological ionic strength is shifted from pH 5.0 to pH 7.4.

**Morphological characterisation of the supramolecular nanorods via electron microscopy**

We performed conventional negative stain transmission electron microscopy (TEM) and scanning transmission electron microscopy (STEM) experiments in order to investigate the morphology of the supramolecular polymers based on monomers 12 and 18. Negative stain TEM images were...
recorded after depositing a 1 mg/mL concentrated clear solution of dendritic peptide 12 in 10 mM phosphate buffer at pH 7.4 and 500 mM NaCl on carbon film coated EM grids (Fig. 5A). Note that after deposition, the EM grids were washed with an aqueous 2% w/v uranyl acetate solution for 15 s to remove the inorganic salts and in order to fixate the organic peptidic material, before blotting excess liquid with filter paper. The TEM micrographs clearly show the presence of nanorods with a diameter of approximately 5 nm in diameter and a contour length distribution ranging from about 150 to 200 nm (Fig. 5A). The morphology thereby justifies the terminology of 1D nanorod-like supramolecular polymers. STEM experiments were furthermore performed using the same solution of 12 to investigate the influence of the staining agent and washing steps on the morphology of the nanorods. After omitting the washing and staining procedures, STEM micrographs reveal the presence of nanorods, albeit with a much higher density on the carbon film coated TEM grid (Fig. S4).

In contrast, conventional negative stain TEM experiments of the monomer solution of 12 at pH 7.4 and 0 mM NaCl only shows small nanostructures of around 10 nm in size, which are likely monomers or very small oligomers (Fig. 5B). Screening of the repulsive interactions in the anionic amphiphilic building blocks leads to a monomer-polymer transition at higher ionic strength, as expected based on our previous findings. Note that ionic strength dependent lengths profiles have also been reported in worm-like micellar solutions of charged surfactants. These results are therefore in full agreement with the detailed pH and ionic strength titrations probed via CD spectroscopy.

Finally we were also able to visualise the pH-triggered formation of supramolecular polymers from fluorinated amphiphilic monomer 18. At pH 5.0 and 0 mM NaCl STEM images show the presence of nanorods (Fig. 6). At this pH, the protonation of the dendritic carboxylic acid side chains is likely to favour bundling of the nanorods into thin fibres. By increasing the ionic strength at pH 5.0 from 0 mM NaCl to 500 mM NaCl, the tendency for bundling becomes more pronounced and larger structures were observed in these samples (Fig. S5). In summary, negative stain TEM and STEM experiments corroborate the CD investigations and the pH and ionic strength triggered formation of one-dimensional supramolecular polymers, with a nanorod-like morphology.

Figure 6 STEM image of the dendritic peptide amphiphile 18, deposited on an EM grid covered with an amorphous carbon film from a 1 mg/mL clear solution of 18 in 10 mM phosphate buffer, pH 5.0 and 0 mM NaCl; the scale bar represents 500 nm.

Experimental

Unless stated otherwise, all reagents and chemicals were obtained from commercial sources at the highest purity available and used without further purification. Water was demineralised prior to use. Some solvents were dried using the following drying agents: dichloromethane over sodium hydride, tetrahydrofuran over sodium and benzophenone. Purification via preparative flash column chromatography was carried out using silica gel with an average grain size of 15-40 µm (MERCK). Technical grade solvents that were used as a mobile phase were distilled before use. Analysis of the collected fractions was performed via TLC on silica coated aluminum sheets (60 F254, MERCK). Size exclusion chromatography was carried out using Sephadex™ LH-20 beads (GE Healthcare Bio-Sciences, Uppsala) as stationary phase and distilled methanol as mobile phase or Sephadex™ G-25 beads (GE Healthcare Bio-Sciences, Uppsala) as stationary phase and demineralised water as mobile phase. The NMR-spectra were recorded on the spectrometers AV 300, ARX 300 and AV 400 (BRUKER). All measurements were...
carried out in deuterated solvents. The chemical shift (δ) is recorded in parts per million (ppm) and relative to the residual solvent protons.\(^{36}\) Mass spectra were recorded on the electrospray ionisation spectrometers (ESI) Micro Tof (BRUKER) and Orbif-Trap LTQ-XL (THERMO SCIENTIFIC). Molecules of a high molecular weight were analysed using matrix assisted laser desorption ionization time of flight (MALDI-TOF) spectrometry using an Autoflex Speed (BRUKER). CD spectra were recorded on a JASCO J-815.

For transmission electron microscopy (TEM) investigations, standard 200 mesh EM grids, covered with a carbon coated plastic foil (Pilofilom), were utilized. To render the support film more hydrophilic, the EM grids were plasma cleaned for 30-45 seconds. For sedimentation, 2-3 μL sample material was left 1 min and afterwards the residual material was blotted. Thereafter, the grids were washed once with 2-3 μL 2% w/v uranyl acetate (15 s). Followed by a second blotting step, the sample material was then stained with uranyl acetate for 45 s, blotted and left for air drying. The samples were examined on a Philips CM10 (FEI, Eindhoven, the Netherlands) operated at 80 kV. Electron micrographs were recorded by a side-mounted CCD camera (IDS, Obersulm, Germany) utilizing acquisition software written in LabView.

For scanning transmission electron microscopy (STEM) investigations, EM high-resolution grids were utilised. Here, a holey carbon film is covered with a 2-4 nm thick amorphous carbon film, which acts as a support for the sample material. As in the case for TEM investigations, the grids were plasma cleaned prior to the sample preparation. Since no staining was performed for STEM investigations the preparation protocol was reduced to the following steps: 2-3 μL sample material was left for sedimentation (1 min). Hereafter, grids were either washed briefly with buffer or blotted directly and left for air drying. The samples were examined in a high-resolution mode for scanning electron microscope (S-5000, Hitachi Japan), equipped with a homemade annular dark-field (ADF) detector.

ADF images were taken at 30 kV acceleration voltage.

Full experimental procedures, materials synthesis and characterisation for compounds 1-18 can be found in the Electronic Supplementary Information (ESI).

1H NMR (300 MHz, DMSO-d$_6$): δ [ppm]= 12.18 (brs, 9H, COOH$_2$), 8.69 – 8.52 (m, 3H, NH$_2$), 8.39 – 7.97 (m, 9H, NH and CH$_2$CO$_{(BTA)}$), 7.59 – 6.82 (m, 48H, CH$_2$Ph$_{Ph}$ and NH$_2$), 4.78 – 4.51 (m, 9H, CH$_2$Phe$_2$), 3.75 – 3.41 (m, 36H, CH$_2$CHO$_{Ph}$), 3.05 – 2.64 (m, 18H, CH$_2$Phe$_{Ph}$), 2.47 – 2.33 (m, 18H, OCH$_2$CHO$_2$), 1.37 (s, 81H, CH$_3$). MALDI-MS (positive mode) (DHB [EtOAc]: m/z calcd. for [M+Na]$^+$ 2515.00; found: 2515.00 [M+Na]$^+$).

1H NMR (300 MHz, DMSO-d$_6$): δ [ppm]= 8.70 – 8.55 (m, 9H, NH$_2$), 8.43 – 7.97 (m, 9H, NH and CH$_2$CO$_{(BTA)}$), 7.60 – 6.82 (m, 48H, CH$_2$Ph$_{Ph}$ and NH$_2$), 4.80 – 4.49 (m, 9H, CH$_2$Phe$_2$), 3.67 – 3.44 (m, 36H, CH$_2$CHO$_{Ph}$), 2.90 – 2.58 (m, 18H, CH$_2$Phe$_{Ph}$), 2.47 – 2.33 (m, 18H, OCH$_2$CHO$_2$), 1.37 (s, 81H, CH$_3$). MALDI-MS (positive mode) (DHB [EtOAc]: m/z calcd. for [M+Na]$^+$ 2380.57; found: 2380.71 [M+Na]$^+$).

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Conclusions

In conclusion, we disclose the synthesis of a series of three anionic dendritic peptide amphiphiles. We systematically study the effect of increasing the hydrophobic shielding of dendritic peptide amphiphiles, and the impact on the pH and ionic strength triggered self-assembly. By establishing state diagrams we show that the supramolecular polymerisation is switched off if the apolar hexyl spacer between the dendritic nonaphenylalanines and peripheral carboxylic acid Newkome dendrons is omitted in compound 6, compared to molecule 12.

If the hydrophobic character of the peptide core is increased further by introducing trifluoromethyl groups via straightforward thiol-ene click chemistry in the O-allyl derivatised tyrosine groups of 18, the thermodynamic driving force for self-assembly is increased and the pH-triggered monomer to polymer transition at physiological pH is shifted from pH 5.0 to pH 7.4. Using TEM experiments we have characterised the 1D supramolecular polymers as well-defined nanorods with lengths distributions ranging from from around 100 nm to 500 nm, depending on the exact pH, ionic strength and hydrophobicity of the peptide backbone. We thereby show that by compensating attractive non-covalent interactions and solvophobic effects with repulsive electrostatic forces, a concept we refer to as disguised growth, is a sensitive tool in order to manipulate one-dimensional supramolecular polymerisation processes in water.

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Notes and references

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4. † The state diagrams were plotted from experimental pH and ionic strength dependent data points. The contour plot was generated using the 2D Interpolation/Extrapolation function in OriginPro 9.1. The boundaries are approximately correct for a monomer concentration of 62.5x10^-4 M at 293 K. They are likely to shift, favouring aggregation, when the monomer concentration is increased.

Electronic Supplementary Information (ESI) available: experimental procedures, materials synthesis and characterisation, additional CD data, negative stain TEM and STEM micrographs. See DOI: 10.1039/b000000x/

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