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Tuning supramolecular architectures of KI_4K amphiphiles via varying terminal variations

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ABSTRACT

We report here how to manipulate the self-assembly behavior of KI_4K by the terminal variations. The results demonstrated that both the supramolecular architectures and their corresponding secondary structure can be tuned just by terminal variations. Twisted or helical ribbons with width over the range of 40–50 nm and a bilayed height were dominant for the peptide CH_3CO—KI_4K—COOH due to the hydrogen bonding interactions resulted from the uncapping —COOH. As a comparison, nanotubes with much larger width but only monolayer wall thickness were dominant for CH_3CO—KI_4K—$CONH_2$. As for Fmoc—KI_4K—COOH, the steric hindrance effect can limit the width growth but the π — π stacking interactions can promote further association of the primary aggregate along the height direction to form nanofiber bundles. Both circular dichroism (CD) and Fourier transform infrared spectroscopy (FTIR) results indicated that the CH_3CO—KI_4K—COOH and Fmoc—KI_4K—COOH adopted a mixture of β-sheet and random coil structure while random coil structure was dominant for both CH_3CO—KI_4K—$CONH_2$ and NH_2—KI_4K—COOH. The small angle neutron scattering (SANS) results indicated the basic lamellar structure for both CH_3CO—KI_4K—COOH and CH_3CO—KI_4K—$CONH_2$ but they go through different pathways to form ribbons and nanotubes with varied shape and size. The Thioflavin-T (ThT) results indicated their abilities to enhance ThT fluorescence intensity was possibly correlated with the amount of aggregates in solutions except for the aggregate morphologies. The peptides involved in the present study provide simple molecular models for the investigation of both —COOH and Fmoc— in contribution to varied non-covalent interactions and the final aggregate morphologies.

1. Introduction

Construction of varied morphologies from the self-assembly of small building blocks by bottom-up approach has been the subject of intense study and can be recognized as one of the most powerful way for supramolecular architectures fabrication [1–3]. The key elements in self-assembly includes both the molecular structure and external conditions. The formation of varied nanostructures was resulted from the balance of different non-covalent interactions, including hydrophobic, hydrogen bonding, electrostatic, and also π — π stacking interactions. For traditional surfactants, the self-assembly behavior was mainly determined by the hydrophobic and electrostatic interactions and several general rules have been developed for them, such as vesicles usually formed in catanionic systems or by a single double tailed surfactants [4], the corresponding aggregates usually goes through from micelles to lyotropic liquid crystals with increasing surfactant concentrations [5,6], and etc. The amphiphilic peptides, even though showed great similarities to traditional surfactants, displaying quite different assembly behavior due to the abundant hydrogen bonds resulting from the peptide backbones as well as the terminals [7]. As directed by the hydrogen bonding interactions along the length axis, a variety of 1D nanostructures including twisted nanofibers [8–11], helical ribbons [12–15], nanotubes [16–25] as well as flat ribbons [26–28] were usually formed in peptide based systems and the final morphology of the aggregate was determined from the delicate balance of different non-covalent interactions [29–31]. Such complex balance made it a difficult pursuit to predict the self-assembly morphology from a primary peptide structure and general rules could not be easily developed for peptides. In this aspect, the precise control of the self-assembled morphology from a primary peptide structure remained a great challenge and was still a research project in its early stage.

Over the past few decades, extensive attention has been paid to the structure and formation mechanism of amyloid nanofibers due to their close relation to many human diseases, ranging from Alzheimer's and neurodegenerative diseases [32,33]. The understanding of the formation mechanism of this type of fibrillar morphology has greatly improved particularly through the hierarchical theory in determining the

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elementary β-strands building blocks to the final aggregate morphology. Usually, the formation of basic β-sheets was determined by hydrogen bonding interactions in the length direction and remained closely similar to each other [34]. The major difference of their polymorphism and the final supramolecular architecture was resulted from the hierarchy assembly of the β-sheets along the width and height direction [34–38]. In this aspect, understanding the roles of different chemical groups in contributing to varied non-covalent interactions involved in their polymorphism and determining the β-strands to different supramolecular architectures was quite important to the exploration of the formation mechanism of different 1D nanostructure. Several previous work has indicated that the peptide terminal in the β-strands are involved in the hierarchical higher-order assembly and can greatly affect the final self-assembly morphologies [39–41]. However, how did a certain terminal, especially different cappings, affects the elementary β-strands assembling hierarchically into the final 1D nanostructure was still not well understood. Therefore, in this paper, four different peptides with the same hydrophobic and hydrophilic residues (four I and two K residues) but different terminals were synthesized and their self-assembly behavior were investigated in order to better understand the roles of both —COOH and Fmoc— in contributing to the varied non-covalent interactions and the final supramolecular architectures. Their structures were shown in Fig. 1 and the self-assembly behavior of them were extensively investigated by a combination of cryogenic transmission electron microscopy (Cryo-TEM), negative-staining TEM, Atomic force microscopy, CD, FTIR, SANS, and ThT experiments. The results demonstrated that the terminals have great impacts on the hierarchy and arrangement of the basic β-sheets growth along both width and height direction. Different 1D nanostructure, including twisted or helical ribbons, nanotubes, and nanofiber bundles with varied width and height can be fabricated just by the terminal variation. This work aims to outline the rules of both —COOH and Fmoc— in tuning the aggregate growth along different directions. The mechanistic insight will benefit further research to construct a certain aggregate morphology from a primary peptide structure.

2. Experimental section

2.1. Materials

The peptides $CH_3CO—KI_4K—COOH$, $CH_3CO—KI_4K—CONH_2$, and $NH_2—KI_4K—COOH$ were synthesized on a CEM Liberty microwave synthesizer by using the standard Fmoc solid phase synthesis strategy. For $CH_3CO—KI_4K—CONH_2$, the C-terminus was amidated by using the Rink amide resin and the N-terminus was capped with acetic anhydride before the cleavage from resin. For both $CH_3CO—KI_4K—COOH$ and $NH_2—KI_4K—COOH$, Wang resin was used to leave the C-terminal uncapping and the N-terminus was capped with acetic anhydride for the former. The detailed information for the synthesis and purification procedures has been clearly described in our previous work [31]. $Fmoc—KI_4K—COOH$ and $Fmoc—KI_4K—CONH_2$ was purchased from GL Biochem (Shanghai) Ltd. The high purity (>98%) of all the products were ascertained by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-ToF) and reversed-phase high-performance liquid chromatograph (RP-HPLC) analyses.

2.2. Sample preparation

The fluffy powder was directly dissolved in Milli-Q water to create peptide solutions with concentration of 0.1 mM for $Fmoc—KI_4K—COOH$ or $Fmoc—KI_4K—CONH_2$ and 4.0 mM for $CH_3CO—KI_4K—COOH$, $NH_2—KI_4K—COOH$, or $CH_3CO—KI_4K—CONH_2$. The suspension was then sonicated for about 10 min with further vortex to get the homogenous solutions. Then, the solution pH/pD value was adjusted to 2.0.

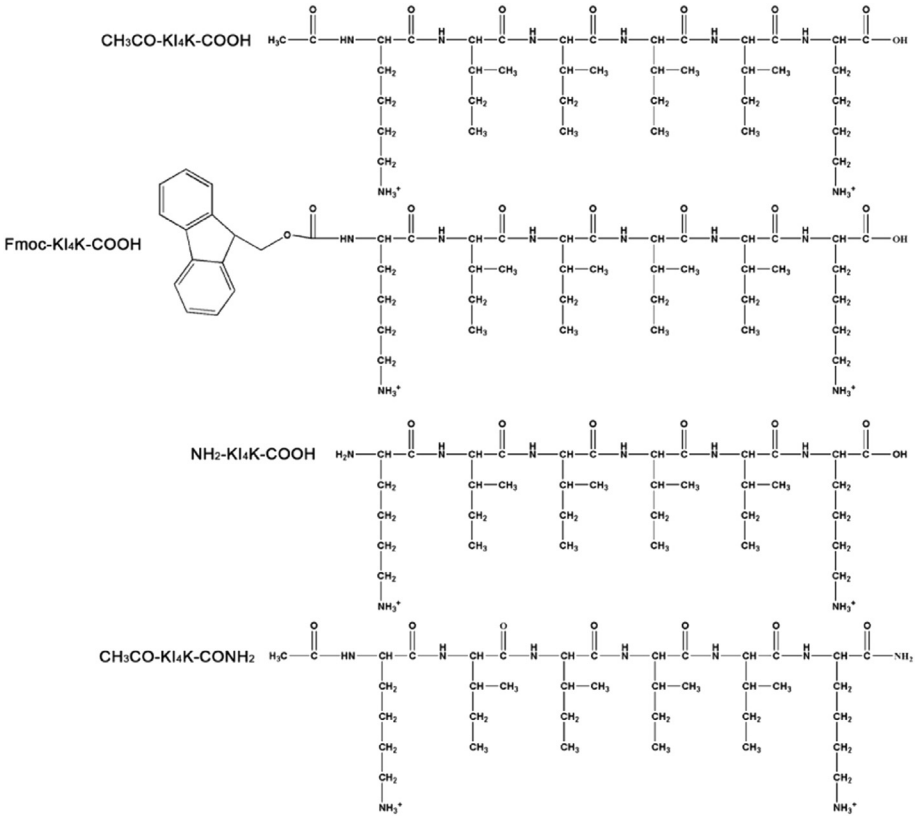

Fig. 1. Molecular structure of $CH_3CO—KI_4K—COOH$, $Fmoc—KI_4K—COOH$, $NH_2—KI_4K—COOH$, and $CH_3CO—KI_4K—CONH_2$. The major difference between each other was the terminal. At pH 2.0, the hydrophilic amino acid side chains and all terminals were 100% protonated. Therefore, $CH_3CO—KI_4K—COOH$, $Fmoc—KI_4K—COOH$, and $CH_3CO—KI_4K—CONH_2$ carried two positive charges while $NH_2—KI_4K—COOH$ carried three positive charges due to the naked N-terminal.