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Self-Assembly

Modulating the Nucleated Self-Assembly of Tri-β³-Peptides Using Cucurbit[*n*]urils

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Abstract: The modulation of the hierarchical nucleated self-assembly of tri-β³-peptides has been studied. β³-Tyrosine provided a handle to control the assembly process through host-guest interactions with CB[7] and CB[8]. By varying the cavity size from CB[7] to CB[8] distinct phases of assembling tri-β³-peptides were arrested. Given the limited size of the CB[7] cavity, only one aromatic β³-tyrosine can be simultaneously hosted and, hence, CB[7] was primarily acting as an inhibitor of self-assembly. In strong contrast, the larger CB[8] can form a ternary complex with two aromatic amino acids and hence CB[8] was acting primarily as cross-linker of multiple fibers and promoting the formation of larger aggregates. General insights on modulating supramolecular assembly can lead to new ways to introduce functionality in supramolecular polymers.

Our understanding of how synthetic peptides and other molecular systems self-assemble into helical structures has progressed in recent decades towards a process that mimics many aspects of nucleated assembly of proteins observed in nature.[1–6] As expected, the nucleated assembly of peptides requires distinct sequence motifs and their assembly can be modulated using conventional factors such as concentration, pH, time, and temperature. More interestingly, the onset and regulation of peptide assembly can be activated by light or enzymatic switches.[7,8] In spite of these advances, the programmability of the hierarchical assembly of synthetic peptides and molecules into higher ordered fibrillar structures remains challenging in contrast to for example, naturally occurring β-sheets that hierarchically assemble into dimers, tetramers, protofibrils, and finally large fibrillar aggregates.[9] In particular, recent research has demonstrated that the addition of chiral auxiliaries or seed molecules can lead to either the exclusive formation of metastable helical aggregates or allows control over fibrillar width and length, as shown in mechanistic assembly studies on aromatic disc- and rod-like molecules.[10–14] Promising results have also been reported by Moore and co-workers to control the final outcome of the nucleated assembly of α-peptides by the addition of polymer-peptide conjugates into discrete nanostructures.[15] Very recently, the addition of macrocycles CB[7] and CB[8] assisted the assembly of functional dimeric and tetrameric proteins, protein wires, and cell clusters mediated by interactions of these macrocycles with aromatic amino acids in proteins.[16–21] Specific CB[7]-phenyl alanine interactions were used by Kim and co-workers to inhibit α-peptide fibril formation[22] and by Urbach and co-workers to inhibit a nonspecific protease.[18]

α-Peptides composed of less than 15 amino acids generally do not adopt defined helical conformations, in absence of structural constraints. In strong contrast, a surprising aspect of β-peptides is that they adopt defined helical structures over very short sequences despite the presence of the additional methylene units, which would be expected to provide the backbone with an increased freedom of orientation.[23,24] β-Peptides, in particular oligomers of β³-amino acids, have evolved as an intensively investigated class of non-biological building blocks for new materials, catalysts, and ligands for protein receptors.[23–31] When properly designed β³-peptides assemble into monomeric 3_{14}-helical structures, a first step toward β-peptide bundle formation. Studies of helical configurations in β-peptides composed of as little as six residues suggested that the assembly proceeds through a nucleation step.[23,32,33] Distinct octameric bundles have been assembled when helical 12-mer β³-peptides were employed in which cationic and anionic side chains were alternated on one helical face, whereas β³-homoleucine residues were introduced on a second helical face.[34,35] Although the assembly mechanism of shorter 3-mer β³-peptides has not been reported so far, no attempts have been made to modulate β³-peptide assembly by addition of molecular components during the nucleation. The ability to modulate the outcome of hierarchically assem-

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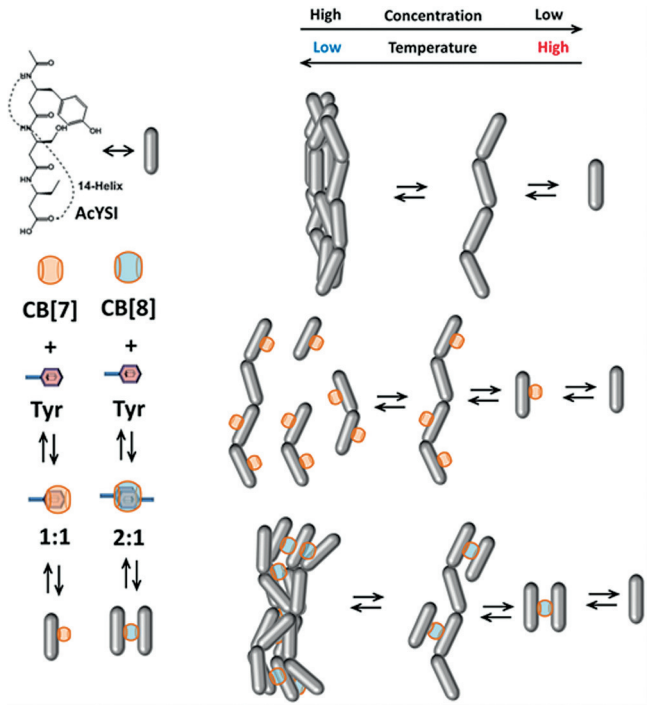
bled structures could open up the ability to post-functionalize the structures and to employ assemblies of particular states as nanomaterials.

Here, we report the nucleated self-assembly of tri-β^3-peptides, composed of three β^3-amino acids, into supramolecular fibrils. The modulating capability of the CB[*n*] on the nucleated self-assembly of tri-β^3-peptides was also investigated. We found that, by varying the cavity size from CB[7] to CB[8], distinct phases of assembling tri-β^3-peptides can be arrested (Scheme 1). Given the limited size of the CB[7] cavity, only one



Scheme 1. Hierarchical assembly of AcYSI.

aromatic amino acid can be simultaneously hosted and hence CB[7] is primarily acting as an inhibitor of self-assembly. In strong contrast, the larger CB[8] can form a ternary complex with two aromatic amino acids and hence CB[8] is acting primarily as cross-linker of multiple fibers and promoting the formation of larger aggregates. The binding constants between β^3-tyrosine with CB[7] or CB[8] were determined by ITC to be $K = 1.4 \times 10^5\ M^{-1}$ (1:1 ratio) and $K = 5.4 \times 10^8\ M^{-2}$ (2:1 ratio), respectively (Figure S13 in the Supporting Information).

A tri-β^3-peptide (AcYSI, Scheme 1) was synthesized following standard procedures (Figures S1 and S2 in the Supporting Information). This short tri-β^3-peptide is known to exhibit six axially oriented hydrogen-bonding interactions facilitating the axial self-assembly during fiber formation, as reported previously by others.[28] In the peptide design, β^3-isoleucine facilitates aggregation by hydrophobic interactions, whereas β^3-serine enhances water solubility. The N-terminus is acetylated (Ac) to prevent formation of charges.

Finally, the presence of β^3-tyrosine in the tri-β^3-peptide further stabilizes the self-assembled structures through π–π stacking leading to the formation of larger fibrillar structures.[28] Importantly, the β^3-tyrosine units also provide a handle to control the assembly process through host–guest interactions with CB[7] and CB[8].

First, the morphological changes upon adding CB[*n*]s to the self-assembled structures of AcYSI were visualized using SEM, AFM, and optical microscopy (Figure 1). All samples were

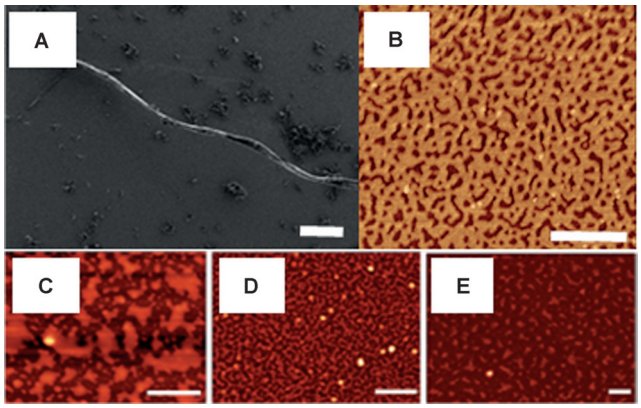


Figure 1. A) SEM image of AcYSI (3.9 mM) and CB[8] (34 μM); B) AFM image of AcYSI (3.9 mM) and CB[7] (34 μM). AFM images of AcYSI alone: B) 0.39 mM, C) 1.5 mM and D) 3.9 mM. Scale bars: A) 100 μm; inset, B), C) and D) 200 nm.

heated to 90 °C and cooled down to 20 °C to facilitate the possible entry of CB[*n*]s within the fibrils during the re-assembly of the peptides before depositing them onto a surface. Inspection of small deposits of concentrated solutions of AcYSI (3.9 mM) on various surfaces showed twisted fibrillar assemblies of several micrometers in length, as readily observed using an optical microscope (Figure S3 in the Supporting Information) and in agreement with observations by others.[28] In contrast, when 34 μM of CB[7] was added to these AcYSI assemblies, small fibrils were detected using AFM (Figure 1 B), whereas larger fibrillar assemblies were observed using SEM upon adding 34 μM of CB[8] (Figure 1 A). Interestingly, fibrils in the presence of CB[8] were larger in width and showed a more extended layered structure in comparison to fibers consisting of AcYSI alone (Figure S4A in the Supporting Information).

Upon diluting the solution of AcYSI (without CB[*n*]s) to 0.39 mM no fibrils were observed, and only ill-defined structures were observed using AFM (Figure 1 C), however, at an intermediate concentration of 1.5 mM, wormlike fibrils were observed across the sample (Figure 1 D). At this intermediate concentration, neither the addition of CB[7] nor CB[8] resulted in differences in assemblies (Figure S4C and D in the Supporting Information). Although isolated large fibrils were present at high concentration (3.9 mM), as imaged with SEM and optical microscopy, smaller fibrils were detected in the background using AFM (Figure 1 E). Based on these measurements, we conclude that the hierarchical assembly of these short tri-β^3-peptides follows three stages. At low concentration, monomeric tri-β^3-peptides exist that predominantly form small fibrils at intermediate concentrations, whereas larger fibrils are formed at

high concentrations. Dynamic light scattering (DLS) measurements verified the involvement of different length scales in the assembly of AcYSI (Figure S5 in the Supporting Information). At a low concentration (0.99 mM) no fibrils were detected, whereas at an intermediate concentration of AcYSI (2.1 mM), aggregates of 141 nm in size were detected. At a high concentration of AcYSI (3.9 mM), larger aggregates of 240 nm were found in addition. Similar observations were made in amyloid assembly studies where protofibrils of intermediate size fuse to form larger, mature fibrils.[36]

To gain further understanding into the mechanism of AcYSI assembly, circular dichroism (CD) spectroscopy was employed (Figure 2). No CD signal was observed in dimethyl sulfoxide

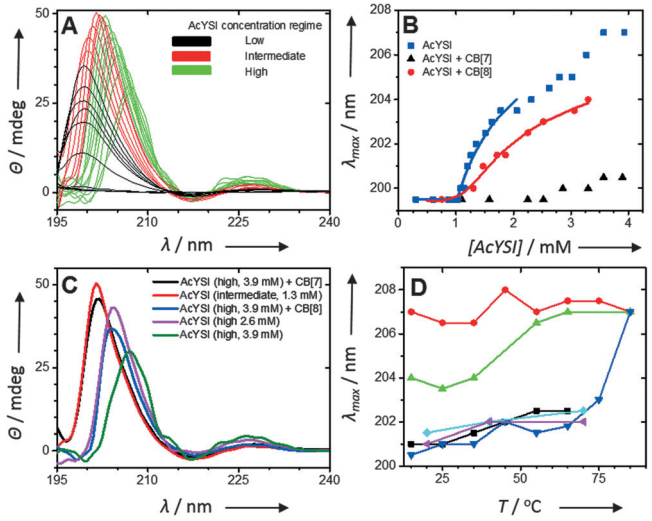


Figure 2. A) CD spectra of AcYSI (PBS, 20 °C) at low (below 1.1 mM, black), high (above 2.1 mM, green) or intermediate concentrations (1.1–2.1 mM). B) λ_{max} of CD spectra (PBS, 20 °C, after heating) plotted vs. AcYSI concentration (■), AcYSI with 34 μM CB[7] (▲) or CB[8] (●). Data is fitted with a nucleation-elongation model (lines, see Supporting Information for details). C) CD spectra of AcYSI (3.9 mM), with 34 μM CB[7] or CB[8] after heating to 90 °C and cooling down to 20 °C (10 °C min^{-1}). CD spectra of AcYSI (1.3 and 2.6 mM) are given for reference. D) λ_{max} of CD spectra plotted vs. temperature for 1.1 (■) and 3.9 mM (●) AcYSI; 3.9 mM AcYSI with 34 μM CB[7] (▼) or CB[8] (▲); 1.1 mM AcYSI with 34 μM CB[7] (◀) or CB[8] (◆).

and ethanol solutions up to a concentration of 3.9 mM of AcYSI, indicating that these solvents do not support the assembly of AcYSI. When 0.30 mM AcYSI solutions were prepared in PBS buffer also no CD signal was observed, indicative of the absence of folded tri-β^3-peptides. In contrast, upon increasing the concentration of AcYSI, the CD signal rose, while simultaneously the wavelength at which the CD intensity has its maximum value (λ_{max}) shifted bathochromically, signaling a gradual assembly of AcYSI into larger aggregates. A decrease in CD intensity and further redshift of λ_{max} was observed upon further increasing the concentration of AcYSI. This is in agreement with previous studies on α-peptides that have shown that desolvation of tyrosine residues due to inclusion of the aromatic group in the hydrophobic core of the fiber during assembly leads to a gradual redshift of λ_{max}.[37,38] Taken together, the changes in CD as a function of AcYSI concentration are supporting the AFM and SEM observations and indicate a hierarchical assembly process of individual monomeric tri-β^3-peptides (low concentration regime) into intermediate protofibrils (intermediate concentration regime) that interact to form mature fibrils (high concentration regime).

When λ_{max} is plotted against the AcYSI concentration (Figure 2B), dilute solutions of AcYSI show no shift of this value up to a critical concentration of 1.1 mM that marks a sudden change in λ_{max}. This observation indicates the nucleation of the assembly process of helically folded peptides to form protofibrils. The concentration-dependent changes in this regime were analyzed using a nucleation–elongation model (Equation 3 in the Supporting Information) assuming a nucleus size of two tri-β^3-peptides, which reveals that the aggregate growth is highly cooperative ($K_e = 0.01$ m M^{-1}). The growth of the protofibrils continues until 2.1 mM. At higher concentrations of AcYSI, up to 3.9 mM, changes in λ_{max} were monitored that deviate from the 1D growth model indicating substantial cross-linking of protofibrils.[6]

Subsequently, the influence of temperature on the AcYSI assembly was investigated. To this end, AcYSI solutions were heated to 90 °C and cooled down at a rate of 10 °C min^{-1} (Figure S6 and S7). In the case of high concentrations (above 2.1 mM) of AcYSI, CD spectra showed no change, indicating that the secondary structure of AcYSI at these concentrations is insensitive to temperature. Yet, in the case of intermediate concentrations of AcYSI (1.1–2.1 mM), no CD signal was found at 90 °C, indicating that protofibrils were disassembled, while from 70 °C to 20 °C the CD intensity gradually restored without hysteresis indicating that the protofibrils were completely reassembled. Figure 2D shows for both concentration regimes a nearly temperature independent λ_{max}. In the intermediate concentration regime (Figure 2D, black), where AcYSI is in the protofibrillar state up to 70 °C, λ_{max} is 201.5 nm, whereas in the high concentration regime (Figure 2D, red), where AcYSI is in mature fibril state, λ_{max} is 207 nm.

Next, either 34 μM of CB[7] or CB[8] was added to AcYSI in the protofibrillar state (intermediate concentration regime, 1.1 mM AcYSI) at 20 °C. No significant shift in λ_{max} was observed when compared to spectra of AcYSI alone (Figures S8A and S9A in the Supporting Information). When CB[*n*]s were added to AcYSI in the disassembled state at 90 °C, after cooling down at 10 °C min^{-1}, the melting curve closely resembled that of AcYSI alone (Figure 2D, magenta and light blue). These results indicate that the macrocycles are not changing the protofibrillar assembly of AcYSI, which is in agreement with AFM data showing the presence of protofibrils (Figure S4C and S4D in the Supporting Information) as were observed for AcYSI (Figure 1D).

To investigate the influence of CB[7] and CB[8] on the mature fibril state of AcYSI, 34 μM of CB[7] or CB[8] was added to AcYSI in the high concentration regime (3.9 mM) at 20 °C. Much to our surprise, addition of CB[*n*]s led to an immediate hypsochromic shift of λ_{max} for both samples (Figures S8B and S9B in the Supporting Information) indicative of hindered maturation of fibrils by CB[7] and CB[8], as these CD spectra closely resemble that of AcYSI alone in the intermediate concentra-

tion regime where AcYSI is in the protofibrillar state. Interestingly, the spectra remained the same for at least 24 h and the shift in λ_{max} depends on the amount of macrocycles added. A CB[*n*]:β-Tyr ratio of 0.001 (4 μM CB[*n*]) appeared sufficient to modulate the assembly pathway (Figure S10 in the Supporting Information).

To examine whether kinetically trapped aggregates were formed, in the next experiment concentrated (3.9 mM) AcYSI solutions were heated to 90 °C and in the presence of 34 μM CB[7] or CB[8] (CB[*n*]:β^3-Tyr ratio of 0.01) cooled down to 20 °C at 10 °C min^{-1} (Figures S8B and S9B in the Supporting Information). The same shift in λ_{max} of the π–π* transition was still observed for CB[7] (Figure 2D, blue), whereas, in strong contrast, for CB[8] λ_{max} only shifted to 204 nm (Figure 2D, green) closely resembling the CD spectrum of AcYSI in the high concentration regime (2.6 mM). These results can be interpreted as follows. The CD spectrum of AcYSI (3.9 mM) in the presence of CB[8] and after heating is comparable to that AcYSI (2.6 mM) in the absence of CB[8] (Figure 2C), which indicates fibrils were formed with less intimate contacts were formed compared to AcYSI alone at 3.9 mM. This is in agreement with SEM images that showed a more extended layered fibril formation in the presence of CB[8] (Figure S4 in the Supporting Information). These observations suggest that mature fibrils can form in the presence of CB[8], but that these fibrils are locally frustrated due to intercalation of CB[8], similar to that observed previously in the case of assembling cross-linked rod-like molecules.[39] When compared to the sample prior to heating, the CD spectrum of AcYSI and CB[8] resembles that of intermediate concentrations of AcYSI alone, indicative of the protofibrillar state (Figure 2C). In contrast, in the case of CB[7] a much larger hypsochromic shift to $\lambda_{max} = 201$ nm was observed, indicating that CB[7] successfully suppresses the formation of mature fibrils, as witnessed by the match of λ_{max} with that of AcYSI alone at intermediate concentrations (Figure 2C). AFM inspection revealed, in this case, similar structures (Figure 1B) to those observed for AcYSI in the intermediate concentration range. These results clearly show that CB[7] and CB[8] have distinct influences on the assembly of AcYSI in the high concentration regime. In contrast to CB[8], CB[7] can only bind a single tyrosine unit, as was confirmed by isothermal titration calorimetry (ITC). As such it can inhibit the lateral assembly of protofibrils into mature fibrils, thus arresting the assembly in the protofibrillar stage. Irrespective of temperature ramping, CB[7] can stably arrest the photofibrillar state, whereas CB[8] can cross-link these into larger fibrils depending on the equilibrating conditions.

To further investigate the modulation of the AcYSI assembly, we measured CD spectra of a series of solutions of AcYSI (0.59 to 3.9 mM) in the presence of CB[*n*] (CB[*n*]:AcYSI ratio remained constant, Figure S11 in the Supporting Information). Figure 2B shows the change in λ_{max} against AcYSI concentration, revealing that the presence of CB[*n*]s yields distinct shifts of λ_{max} with a strong difference between CB[7] and CB[8]. The assembly of AcYSI in the presence of CB[8] nucleated at the same concentration as AcYSI alone; however, the cooperativity was less ($K_e = 0.7$ mM^{-1}). Also, the CD intensity is lower and λ_{max} is blueshifted, indicating that complexation with CB[8] leads to less extended order of the fibrils, which is in agreement with SEM images in Figure S4 in the Supporting Information. In the case of AcYSI in the presence of CB[7], nucleation-elongation is suppressed efficiently; some higher order assembly takes place only above 2.5 mM. Solutions of AcYSI (high concentration) and AcYSI with CB[8] also showed markedly higher viscosities compared to solutions with CB[7] similar to intermediate solutions of AcYSI (Figure S12 in the Supporting Information). This observation further corroborated that the macrocycles are interfering with the assembly of AcYSI, suggesting that, in the case of CB[8], a cross-linked network is formed that is not present in the case of CB[7]. This difference can be related to the possibility of CB[8] for binding two β^3-tyrosines from opposite sides of the cavity, thus serving as a cross-linker between two protofibrils and yielding more viscous samples when compared to CB[7], in which case the mono-Tyr binding inhibits the lateral interaction of peptide fibrils. These observations are in good agreement with findings from the morphological study where large fibrils were observed in the case of CB[8], whereas in the presence of CB[7] no large fibrils were detected.

In conclusion, the results demonstrate that the self-assembly process of short trimeric β^3-peptides can be modulated by addition of CB[*n*]s. We achieved different phases of chiral assemblies by controlling the lateral interactions of peptide protofibrils. General insights on modulating supramolecular assembly[40] can lead to new ways to introduce functionality in supramolecular polymers.

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Keywords: cooperativity · cucurbit[*n*]urils · host–guest systems · self-assembly

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