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Direct monomer-to-fibril assembly of a β-hairpin peptide:
A dynamic circular dichroism study

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It is now well established that under certain conditions, proteins and peptides can form amyloid fibrils outside pathological context to fulfill a beneficial role\(^\text{1,2}\); in particular, peptide hormones form reversible amyloid aggregates for storage purpose.\(^\text{3}\) Although the interactions driving the assembly of reversible functional amyloids are similar to those of pathological amyloids (i.e. a balance between hydrogen bonds, hydrophobic and electrostatic interactions), the mechanisms and dynamics of assembly of functional amyloids have been less thoroughly studied and it is not clear in which respect they may differ. Indeed, while the formation of pathological amyloids is kinetically controlled, the formation of reversible functional amyloids is clearly resulting from thermodynamic equilibriums.

In the present work, we study the self-assembly properties of Atosiban, a nonapeptide drug whose sequence is very close to those of the oxytocin and vasopressin hormones. We show that this very soluble peptide consistently self-assembles into 7-nm wide amyloid fibrils above a critical aggregation concentration (2-10%\text{w/w} depending on the buffer conditions). The peptide system is fully characterized from the monomer to the assembled form with osmotic concentration measurements, transmission electron microscopy, small angle x-ray scattering, infrared and fluorescence spectroscopy, and synchrotron radiation circular dichroism. We have monitored the fibrils assembly in situ with fluorescence spectroscopy and synchrotron radiation circular dichroism and noticed that the peptide undergoes conformational changes during the process. However, all evidences point towards a one-step, direct association of monomers into fibrils without passing through oligomeric intermediate species contrary to what is usually reported for pathogenic amyloids. The native β-hairpin conformation of the monomer could explain the straightforward assembly. The tyrosine stacking is also shown to play an important role. We propose a packing model that accounts for the experimental observations.

References