

Amyloid Fibres Formed from the Self-Assembly of an Arginine/Phenylalanine Oligopeptide*

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Introduction

Peptide fibrillization is a relevant topic often associated to neurodegenerative disorders such as Alzheimer's, Parkinson's and Huntington's diseases. Understanding the mechanisms involved in the aggregation process is an important step toward the development of strategies for control and treatment. In this work, a model sequence composed exclusively of arginine and phenylalanine, the octapeptide RFRFRFRF (RF8), has been synthesized and its fibrillization, investigated. The self-assembly was evaluated and many features of amyloid-like analogs such as the canonical cross- β structure and the formation of intermediate aggregates during the fibrillization pathway have been identified. Particularly, the structure of these species has been investigated in detail through the combination of highly-resolved fibre XRD and *in situ* analysis using small-angle X-ray scattering. The findings presented here are the first detailed report on the self-assembly and structure of amyloid-like analogs from binary simplified oligopeptides based on arginine moieties.

Results and Discussion

Fluorescence and UV-Vis assays were used to determine critical aggregation concentrations, corresponding to the formation of oligomeric species and β -sheet rich structures organized into both spheroidal aggregates and highly-ordered fibrils. TEM and AFM images showed globular aggregates and long unbranched fibres with diameters ranging from ~ 4 nm up to ~ 40 nm. FTIR and circular dichroism spectroscopy confirm the presence of β -sheet structures and X-ray fibre diffraction on oriented stalks provides detailed information on the structure of the fibres indicating peptide organized into layers based on an orthorhombic unit cell, Fig. 1. *In situ* small-angle scattering (SAXS) shows the presence of low molecular weight oligomers in equilibrium with mature fibres which are likely made up from 5 or 6 intertwined proto-filaments.

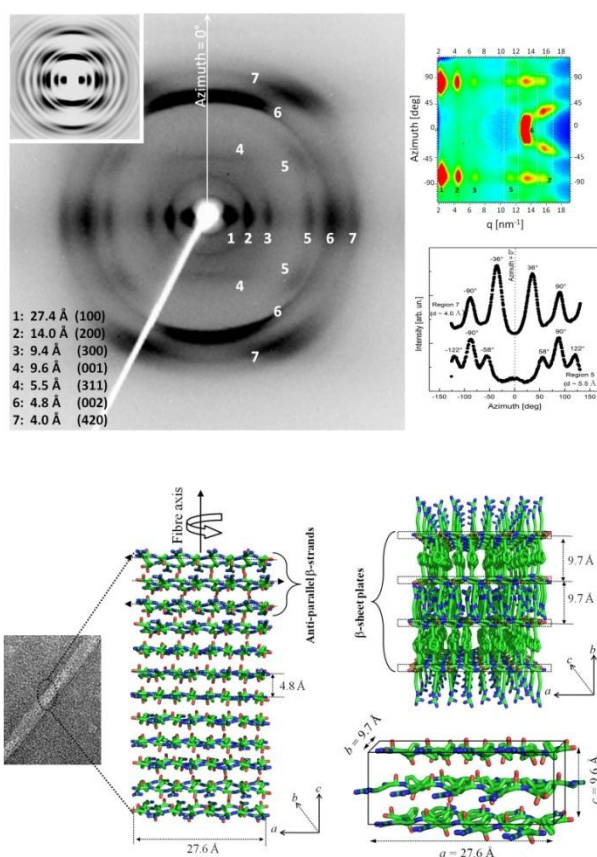


Figure 1. Top: XRD pattern obtained from oriented RF8 fibres. Bottom: structural model for amyloid fibrils arising from the combination of diffraction and spectroscopy data.

Conclusion

Our results show that the RF8 octapeptide is a useful model peptide, with a highly simplified sequence, incorporating dual functionality from aromatic and cationic residues, that forms amyloid-type β -sheet rich fibrils and other amyloid-like analogs along its self-assembly pathway.

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