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Conformational Polymorphism of a Fibrillogenic Fusion Peptide in Explicit Solvent and at an Interface

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The development of therapeutic agents against amyloid diseases requires an understanding of the conformational properties of fibrillogenic species on a microscopic level. Here we have used molecular dynamics simulations to study the fibrillogenic fusion peptide B18 in monomeric form in various environments. In particular, our results indicate that B18 forms β-sheet/coil conformations in water, whereas adsorption at a water/vapor interface induces α-helical conformations. α-β transition pathways in water are suggested. Our results show that previous spectroscopic measurements reflect properties of monomers and reveal a pronounced conformational polymorphism of B18 in different environments, thus highlighting the need for an explicit description of the solvent environment in order to understand fibrillogenic species from molecular dynamics simulations.

1 Introduction

A number of neurodegenerative diseases such as Alzheimer's are associated with the conversion of proteins from a soluble, functional form into a β-rich structure that is highly prone to aggregate into toxic oligomers or so-called amyloid fibrils. The conformational transition is believed to take place in a partially denaturing environment of a cellular compartment either in solution or at an interface. Hence, the development of therapeutic agents against amyloid diseases requires an understanding of the conformational polymorphism in different environments on a microscopic level. To study fibrillogenic species experimentally in atomic detail is difficult because of their tendency to aggregate. Therefore, an indispensable tool to study these systems is provided by computer simulations. Here we have chosen the 18-residue peptide B18, a fragment of the sea-urchin fertilization protein Bindin[1] as a model system. The amphiphilic sequence of the peptide is shown in Fig. 1 (a). B18 forms amyloid fibrils *in vitro*. The soluble form in water forms β-sheet and coil structures with increased β-sheet content in the presence of NaCl as indicated from circular dichroism (CD) spectroscopy. Addition of trifluorethanol (TFE) or adsorption of B18 at a water/air interface induce α-helical conformations as indicated from CD or infrared reflection absorption spectroscopy (IRRAS), respectively, the latter suggesting helices to be parallel to the interface.[2,3] Nuclear magnetic resonance (NMR) measurements indicate a helix-kink-helix motif for B18 in water/TFE with 70:30 volume fractions[2] as shown in Fig. 1 (b). No detailed structure is available for B18 in pure water in the presence or absence of NaCl or at a water/air interface. In fact, it is not even clear to which extent conformations indicated from CD or IRRAS arise from mono- or oligomers. We have used molecular dynamics (MD) simulations to study B18 in monomeric form in explicit solvent and interfacial environments on a microscopic level.[4]

Figure 1. (a) Amino acid sequence and (b) structural model for B18 in a water/TFE 70:30 (volume fractions) mixture based on NMR data[2] in ribbon representation. The color code distinguishes between hydrophobic (*yellow*) and hydrophilic (*blue, green, and red*) residues.

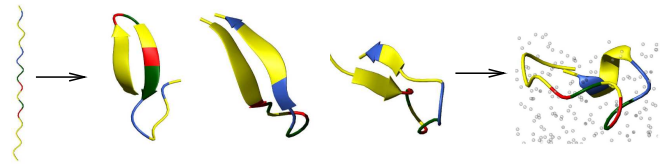

Figure 2. Initial configuration ("initial"), typical β-sheet conformations of B18 in water ("water 1 – 3"), and representative conformation at a water/vapor interface ("water/vapor"). The representation is similar to that chosen in Fig. 1 (b). In "water/vapor", positions of water oxygens are indicated as gray dots.

2 Methods

B18 in explicit water/TFE with 70:30 volume fractions, pure water in absence and presence of 100 mM NaCl, and at a water/vapor interface with vapor modeling air were studied using periodic boundary conditions. Initial peptide configurations were a helix-kink-helix as in Fig. 1 (b), an extended as in Fig. 2 (*initial*) or a β-sheet/coil conformation as in Fig. 2 (*water 3*). Typically, three 50 ns simulations using the same initial peptide configuration, but different sets of initial velocities were performed. Most simulations were carried out at 293 K to mimic experimental conditions. Simulation details are given elsewhere.[4]

3 Results and Discussion

B18 in water/TFE with 70:30 volume fractions, pure water in the absence or presence of 100 mM NaCl, and at a water/vapor interface with vapor modeling air were studied. During simulations started from extended peptide configurations as in Fig. 2 (*initial*), coil and β-sheet conformations as in Fig. 2 (*water 1 – 3*) were adopted. β-sheets were mainly formed by hydrophobic residues, see Fig. 2 (*water 1 – 3*) (*yellow*). Addition of NaCl led to an increase in the average β-sheet content. Various β-sheets containing different residues were observed. β-sheets formed twice in independent simulations, suggesting that they are typical structures in water, are shown in Fig. 2 (*water 1 – 3*).

Pre-formed α-helical conformations as in Fig. 1 (b) were more stable in water/TFE or at a water/vapor interface than in pure water. In general, α-helical conformations were more stable in the C-terminal than the N-terminal half of the peptide. In water at 350 K, transitions from α-helical into β-sheet conformations where observed as shown in Fig. 3.

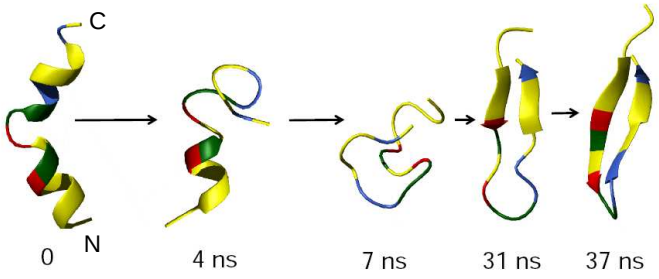

Figure 3. α-β transitions of B18 in water at 350 K. The representation is similar to that chosen in Fig. 1.

The C-terminal and, after 7 ns, the N-terminal helix dissolved in two independent simulations. Thereafter, the peptide underwent a transition from a compact coil as in Fig. 3 (*7 ns*) to more extended β-sheet conformations, see Fig. 3 (*31 – 37 ns*). The occurrence of a compact coil intermediate is similar to what has been observed during α-β transitions of other sequences in previous simulations, see references in[4], suggesting a universal feature for α-β transitions.

A peptide in β-sheet/coil conformation as in Fig. 2 (*water 3*) placed next to a water/vapor interface was spontaneously adsorbed at the interface. At the interface, the amount of β conformations decreased, and α-helical conformations formed in the C-terminal half of the peptide in two out of three simulations (compare Fig. 2 (*water/vapor*) and Fig. 1), suggesting early conformational transitions after adsorption. In all simulations of B18 at water/vapor interfaces, α-helical segments were approximately parallel to the interface.

4 Conclusion

Our results on the conformation of monomeric B18 in water and at a water/vapor interface and the interfacial orientation of the peptide are in agreement with available spectroscopic data and, thus, indicate these data to reflect properties of monomers. In addition, our simulations give insights into conformational distributions and transition pathways on a microscopic level. Revealing a pronounced conformational polymorphism of B18 in different environments, our work highlights the need for an explicit description of the solvent environment in order to understand fibrillogenic species from MD simulations.

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