Peptide Folding, Aggregation, and Adsorption at Interfaces

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A number of neurodegenerative diseases such as Alzheimer's or Parkinson's are related to the precipitation of protein into β-sheet rich amyloid fibrils. The transformation of a protein from the functional soluble state to the pathogenic fibril state is believed to be initiated by a misfolding of the protein and the formation of small oligomers. Interfaces can promote or inhibit fibril formation depending on the amino acid sequence of a peptide and the molecular structure of the interface. To study the early steps of fibril formation in atomic detail experimentally is difficult due to the tendency of misfolded proteins to aggregate and the short lifetimes of small oligomers. Computer simulations therefore provide an indispensable tool to study these processes.

We employ molecular dynamics simulations to study fibril forming peptides in solution and at interfaces as model systems. In our simulations, peptide(s) and solvent environment are described in atomic detail. Atoms are modeled as classical point masses whose interaction is described using a semi-empirical force field. The simulations provide a high spatial and temporal resolution of biomolecular processes. However, due to their computational expense such simulations suffer from a notorious sampling problem. Therefore, experimental data are important bench-marks for the simulations. In a collaboration with the group of Gerald Brezesinski from the interfaces department, we have studied the fibrillogenic peptide B18, a fragment of the sea urchin fertilization protein Bindin and corresponding to resides 103-120 of the parent protein **[1-3]**.

In water, B18 tends to form β-strand-loop-β-strand conformations (see Fig. 1(a) *middle*). β-sheets are mainly formed by hydrophobic residues (*yellow*). In the initial steps of the adsorption at a water/vapor interface, α-helical and turn conformations are induced in the C-terminal segment which is partially hydrophilic (see **Fig. 1(a)** right) **[1]**. Upon adsorption to a (negatively charged) DPPG monolayer, B18 becomes somewhat more disordered. The effect of the environment on the peptide structure is in agreement with data from circular dichroism (CD) and infrared spectroscopy **[2]**. For the first time, we have studied the formation of partially ordered dimers of strand-loop-strand forming peptides in explicit solvent (see **Fig. 1(b)**) **[3]**. Whereas previous simulations using implicit solvation models predicted planar aggregates, we observe highly twisted β-sheet structures, indicating the twist to be (partially) a specific solvent effect.

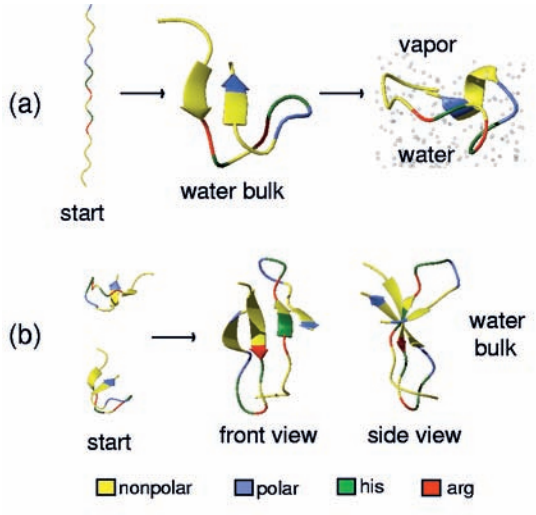

Fig. 1: Folding and aggregation of B18 peptide in different environments in molecular dynamics simulations. (a) In water, B18 tends to adopt β-strand-loop-β-strand structures (middle). Adsorption to a water/vapor interface induces α-helical conformations (right). (b) In water bulk, partially ordered β-sheet rich dimers can form on a nanosecond timescale. The peptide backbone is shown in ribbon representation, the amino acid sequence is color-coded.

In water, pre-formed α-helical conformations are partially kinetically trapped on the nanosecond timescale of our simulations at room temperature, but convert into β-sheet structures at elevated temperature as shown in **Fig. 2**. The transition is initiated by a quick hydrophobic collapse (see **Fig. 2(c,d)**). α-helical conformations dissolve into turn and coil conformations (see **Fig. 2(a,b)**) and the number of main chain hydrogen bonds decreases (see **Fig. 2(e)**). Upon formation of β-sheets (see **Fig. 2(b)**), the peptide becomes more extended again (see **Fig. 2(c)**).

A water/vapor interface stabilizes α-helical conformations in agreement with infrared data. This finding allowed the usage of a coarse grain model in which the peptide was described as a rigid helix and facilitated to study the lateral organization of multiple B18 peptide and DPPC molecules in the interface. As shown in **Fig. 3**, B18 and DPPC demix in the interface and B18 accumulates in the three-phase boundary between water, lipid, and vapor phase. At the equilibrium lateral pressure (known from experiment), the interface is fully covered by peptide and lipid molecules which remain demixed (see **Fig. 3**, right). The demixing of B18 and DPPC molecules in a water/vapor interface explains the experimental observation that adsorption of B18 to a DPPC monolayer in the liquid-expanded gas coexistence region does not change the structure of the DPPC monolayer **[1]**.

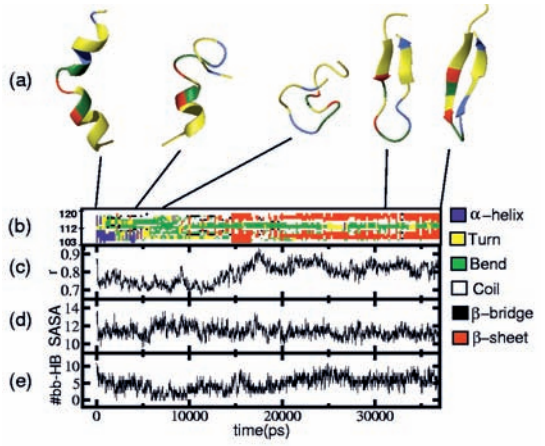

Fig. 2: α-β transition of B18 in water at elevated temperature involving a compact coil intermediate. (a) selected configurations. (b) Time evolution of the secondary structure obtained from an analysis of backbone hydrogen bonds. Here the vertical coordinate represents the residue number which is plotted against time, and the secondary structure is color-coded. (c-e) Time evolutions of (c) radius of gyration (measure of compactness of the peptide), (d) hydrophobic solvent-accessible surface area (measure of the exposure of nonpolar groups to the solvent), and (e) number of peptide main chain hydrogen bonds.

Future Work

Ongoing work is focused on (i) sequence effects on the folding and aggregation of amyloid forming peptides, (ii) membrane fusion, and (iii) electrokinetic phenomena. PhD student Madeleine Kittner who started at the beginning of January 2007 will work on peptides. Another member starting in the coming months will work on membrane fusion. A PhD student starting in February 2007 will work on a new project, (iv) modeling of molecular motors with atomic resolution. Besides these molecular dynamics studies, (v) a mesoscopic study of pore formation in membranes is carried out by the postdoc Josep Pamies.

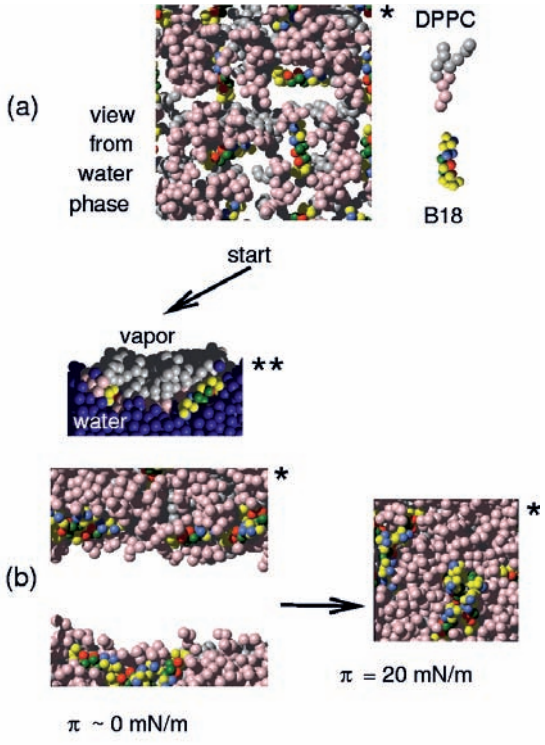

Fig. 3: Demixing of B18 peptide and DPPC lipid molecules in a water/vapor interface in simulations using a coarse grain model. (a) As initial configuration, a random distribution of molecules in the interface was used. (b, left) During a simulation peptide and lipid molecules demix spontaneously. Peptides accumulate in the three phase boundary between water, lipid, and vapor. (b, right) At the equilibrium lateral pressure (known from experiment), the interface is fully covered by peptide and lipid molecules which remain demixed. Views of configurations normal to the interface towards the vapor phase (*) or parallel to the interface (**) are shown.

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References:

[1] V. Knecht, H. Möhwald, and R. Lipowsky, Conformational diversity of the fibrillogenic fusion peptide B18 in different environments from molecular dynamics simulations, J. Phys. Chem. B, **111**, 4161-4170, 2007

[2] E. Maltseva, Model membrane interactions with ions and peptides at the air/water interface, Ph.D. thesis, Universität Potsdam (2005).

[3] V. Knecht and R. Lipowsky, Dimerization of the fibrillogenic peptide B18 in water in atomic detail, in preparation.