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REMD Simulations of Aβ_{16-22} Peptide Aggregation in Explicit Solvent

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Experimental studies show that the short peptide fragments Aβ_{16-22} form fibrils as it is known from the full length β-amyloid peptide. This fibril growth is strongly temperature dependent. We report here a simulation study of the temperature dependent Aβ_{16-22} aggregation in explicit water. We simulated a system of ten Aβ_{16-22} peptides with 5900 SPC/E water in a cubic box and used 76 replicas (with 20 ns simulation time per replica) distributed over a temperature range from 285.0 to 606.3 K. Replica Exchange Molecular Dynamics (REMD) simulation is an efficient way for equilibration and simulation of complex molecular systems at different temperatures. The temperature dependence of radius of gyration R_G and the solvent accessible surface area(SASA) of the aggregates, as well as structural properties like mutual orientation and number of peptide-peptide hydrogen bonds can be understood by the different temperature dependence of hydrogen bond strength, electrostatic, and hydrophobic interactions.

The Aβ_{16-22} fragment is highly prone to aggregation, and a prototype molecule for the study of processes of amyloidosis. It contains a central hydrophobic core, a positive charge at the N-terminus (Lys16), and a negative charge at the C-terminus (Glu22). Solid-state NMR showed that this segment of the full amyloid-β peptide can form fibrils with an antiparallel strand organization.[1] Experimental studies of Aβ fibril formation also revealed a strong temperature dependence.[2] This could also be obtained in constant pressure MD simulations of Aβ_{16-22} peptides aggregation.[3] Here we present first results of an extension of this study, where we apply Replica Exchange Molecular Dynamics (REMD) simulations. This is an efficient way to simulate complex systems at different temperatures and is the simplest and most general form of simulated tempering.[4] It offers a much-improved approach for determining oligomer distributions relevant to aggregation.[5] The basic idea of REMD is to simulate different copies (replicas) of the system at the same time but at different temperatures. After a certain time, conformations are exchanged with a Metropolis probability, therefore permitting random walks in the temperature space and escape from local energy traps.[6] Recently, Paschek et al.[7] published such simulations, providing the first unbiased folding of the Trp-cage in explicit solvent using 40 replicas (100 ns per replica).[7]

Taking Paschek et al. work as a reference,[7] we used REMD to study Aβ_{16-22} peptides aggregation at atomic level in explicit aqueous solution.[8] The GROMACS 3.2.1[9] simulation package was used in both simulation and data processing. The OPLS-All Atom force field was chosen to represent the peptide in GROMACS. The system is coupled to an external heat bath (Nose-Hoover-thermostat) with a relaxation time of 1.5 ps. The electrostatic interactions are treated by the smooth particle mesh Ewald summation with a real space cutoff of 0.9 nm. A 2.0 fs timestep was used for all simulations. Solvent constraints were solved using the SETTLE procedure, while the SHAKE-algorithm was used for the polymer constraints.

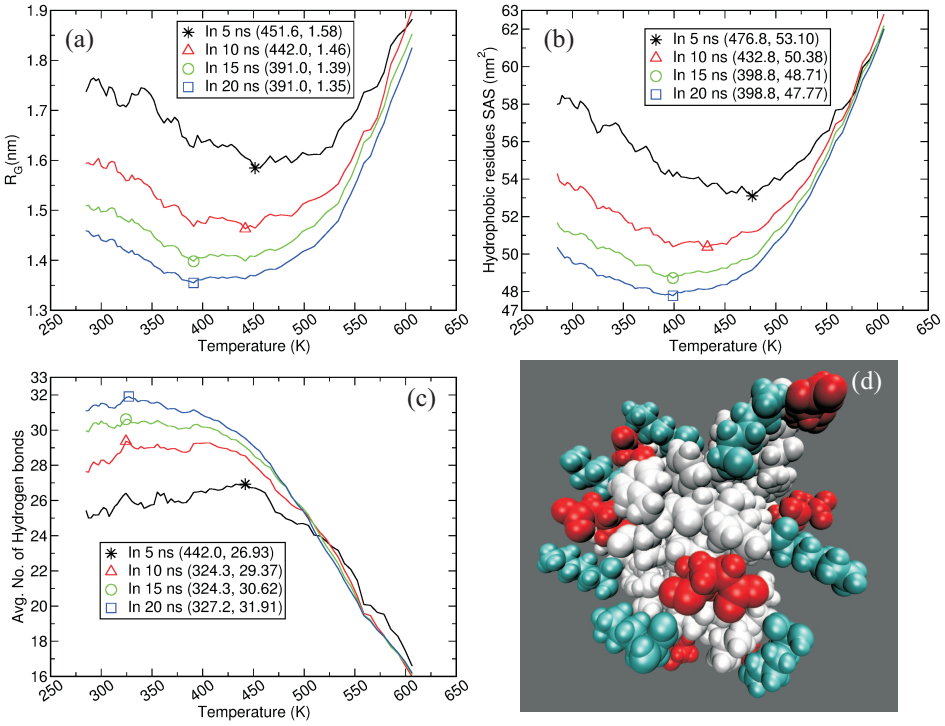

Figure 1. Properties of the peptide aggregates, averaged over different lengths of the simulation runs as a function of temperature. Lowest/highest values are marked. (a) Radius of gyration R_G of the peptide back-bone atoms. (b) SASA of hydrophobic residue atoms. (c) Average number of hydrogen bonds between the peptides. (d) Final snapshot at 398.8 K, hydrophobic residues in white, Lys(+) in cyan and Glu(-) in red.

In the starting configuration of this study, as in the previous constant pressure simulation series[3], six monomeric peptides (Capped Aβ_{16-22} with the sequence of Ace-KLVFFAE-NH_2) were placed uniformly in a distance of about 1.5 nm around the center of an ordered tetramer which was considered to serve as nucleus for further growth. It was obtained in an initial constant pressure simulation of four peptides at 360 K after 20 ns.[3] These 10 peptides are immersed in 5900 SPC/E water molecules in a $5.8 \times 5.8 \times 5.8(\mathrm{nm})^3$ cubic box and periodic boundary conditions were applied. For REMD we used 76 replicas (20 ns per replica) distributed over a temperature range from 285.0 to 606.3 K, where multiple copies (or replicas) of identical systems are simulated in parallel at different temperatures. The temperature spacing between each of the replicas was chosen such that the energy distributions overlap sufficiently and state exchange attempts are (on average) accepted with a 20 % probability.

The results from our constant pressure simulations (at seven temperatures from 280 to 460 K) show that the Aβ_{16-22} monomers first form anti-parallel hydrogen-bonded dimers at the lower T range of 280–340 K. These aggregate at middle T range from 340 to 400 K, to large structures, which show two major features of the amyloid fibrils: twisted β-sheets

formed from antiparallely oriented peptides and the onset of formation of a second layer. In the higher temperature range (from 400 to 460 K) the twist angle between the monomers increased probably to protect hydrophobic residues from water.[3]

From the REMD simulations, properties of interest have been extracted at 76 temperatures. Below 391 K, the radius of gyration R_G of peptide cluster (calculated from peptide backbone atoms) decreases with increasing temperature, and started to increase with T below 391 K [Figure 1(a)]. Consequently, also the SASA calculated from the hydrophobic residues, reached a lowest point at a temperature 398 K [Figure 1(b)]. Figures 1(a and b) show that the aggregated structures at intermediate temperatures extend and disintegrate at high temperatures. The maximum number of peptide–peptide hydrogen bonds is observed at around ~ 330 K and decreases at higher temperatures [Figure 1(c)]. The shift of the positions of the minima of R_G and SASA compared to the maximum of the number of H-bonds can be explained by the fact, that with increasing temperature the H-bonds are weakened, whereas the hydrophobic interaction strength increases. While the H-bonds tend to build a planar β-sheet structure, the increasing hydrophobic interaction produces more compact structures [Figure 1(d)]. This may be obtained by twisting the β-sheet or by building up a second sheet, as observed in the constant pressure simulation study.[3] Interestingly, Meinke and Hansmann[10] also observe for a system of six β-amyloid fragment peptides (without explicit water) above 400 K a strong increase of R_G, but do not observe a temperature minimum. This is probably due to the lack of water (and the water mediated hydrophobic interaction) in their simulations. To demonstrate the convergence of the REMD simulations, in figures 1(a, b and c) averages over different lengths of the simulation runs (5, 10, 15 and 20 ns) are shown and the minima and maxima are marked. From 15 to 20 ns the positions of there extrema on the temperature axis stay a constant, revealing that 20 ns time for each replica is reasonable to study early aggregation.

Our results are in good agreement with the previous work done by Meinke et al.[10] and Gnanakaran et al.[5]. We find that at low temperatures the structure of the aggregates is largely determined by hydrogen bonding and electrostatic interactions. This leads to the formation of well ordered antiparallel β-sheet structures. With increasing temperature, hydrophobic interactions become more important, as indicated by the formation of stacked β-sheets, as well as less regular ordered collapsed clusters. At highest temperatures the aggregates are found to disintegrate due to the strong thermal motions.

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