Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.

Supporting Information

Dose-dependent binding behavior of anthraquinone derivative purpurin interacting with tau-derived peptide protofibril

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A series of MD simulations were performed to investigate the dose-induced influence of purpurin on the protofibril stability of another aggregation-prone fragment PHF6*, further examining the influence of the residue sequence on the power law behavior of purpurin binding. The results presented in Fig. S1 quite resemble with those of PHF6, and here purpurin has less preference for amino acids because the PHF6* segment contains no aromatic residue. The power law binding behavior of purpurin to PHF6* protofibril is not affected, because the power property originates from the self-assembly of purpurin, which is still observed.

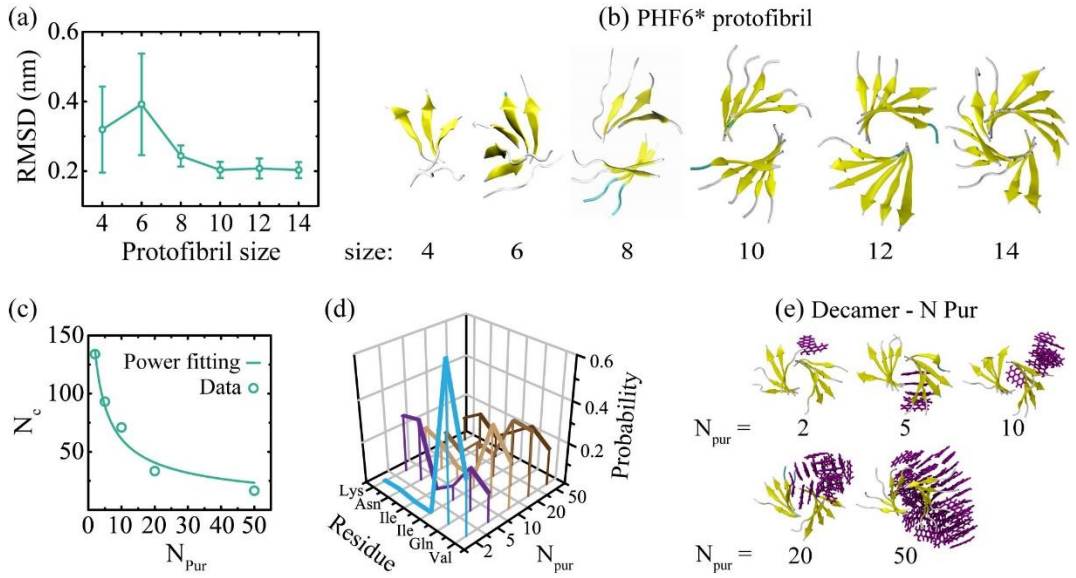

Fig. S1 (a) RMSD as a function of protofibril size of PHF6* oligomers. (b) Snapshots of protofibril oligomers with different sizes at the simulation time of 0.5 μs. (c) N_c as a function of N_{pur} shows the power law behavior from the simulation data (open circles). Power fitting is $y=a(1+x)^b$, where a=273±34, b=-0.625±0.073, and R^2=0.966. (d) Binding probability of purpurins with each residue at different purpurin/peptide ratios. (e) Snapshots of the final structures in all simulated decamer-NPur systems. The peptides are represented in cartoon and purpurins in licorice.

The octamer-1Pur system was simulated using the equilibrated structure rather than crystal structure to model the octamer. The β-sheet content and RMSD reflects that protofibril octamer maintains a good structural stability in the presence of one purpurin. The average value of β-sheet content is 0.61±0.03, very close to the value of 0.62±0.02 for the isolated octamer system. After 0.2 μs of equilibration, more stable contacts were formed between the purpurin molecules and protofibrils, implying a relatively strong binding.

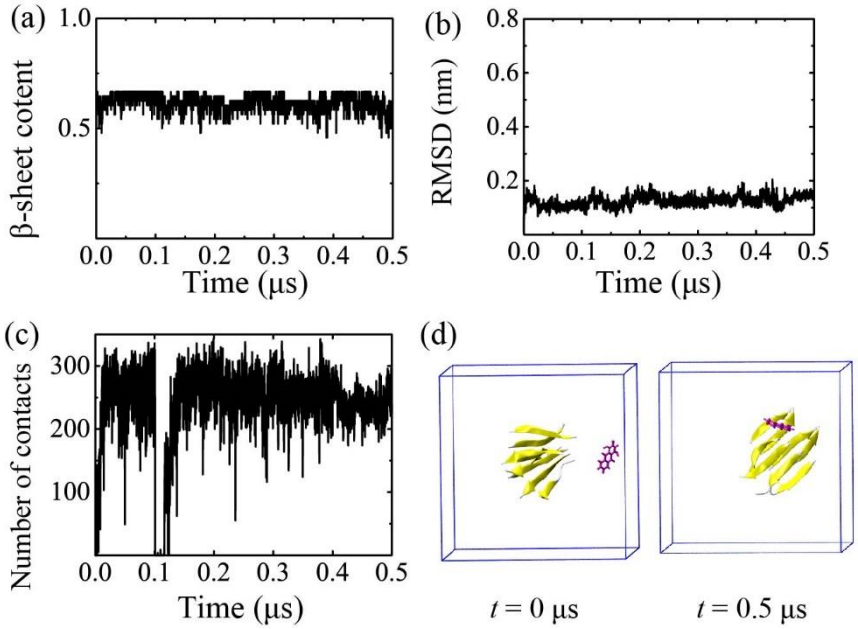

Fig. S2 (a) Time evolution of β-sheet content in the octamer-1Pur system. (b) Time evolution of Cα-RMSD relative to initial structure. (c) Number of contacts between purpurin and octamer as a function of time. (d) Snapshots of the initial and final structures. Here, the equilibrated structure obtained from the final output of the protofibril octamer system, rather than the crystal structure, was used to model the octamer.

The octamer-4Pur system with the equilibrated structure of the octamer was simulated. It was found that the β-sheet content is 0.56±0.03, very close to the value of 0.57± 0.02 for the octamer-4Pur system (initiated from crystal structure) in the main text. The RMSD slightly increases in the last 50 ns of the simulation, because one purpurin molecule inserts between the two β-sheets. Each purpurin molecule has 134±29

contacts, covering the average value of 113 for the octamer-4Pur system used in the text. In addition, the radius of gyration of the purpurin molecules reflects that the 3+1 cluster pattern of purpurin dominates in this simulation trajectory, but the 2+1+1 pattern also appears transiently. The observed single purpurin molecule slightly moves away from the protein surface in the last duration of the simulation, and after reorienting, it inserts between the two β-sheet layers, causing significant disruption to the hydrophobic stacking of the side chains. Interestingly, this disturbance of steric-zipper interface was also observed in the Run 1 of the octamer-4Pur system in the text. Thus, the binding mode of purpurin and its impact on the protofibril oligomer are very similar to the results from the simulation system initiated from the modelled crystal structure. This additional MD simulation further validates that purpurin shows a significant disruptive effect on protofibril nucleus when its molar ratio to peptide is 1:2.

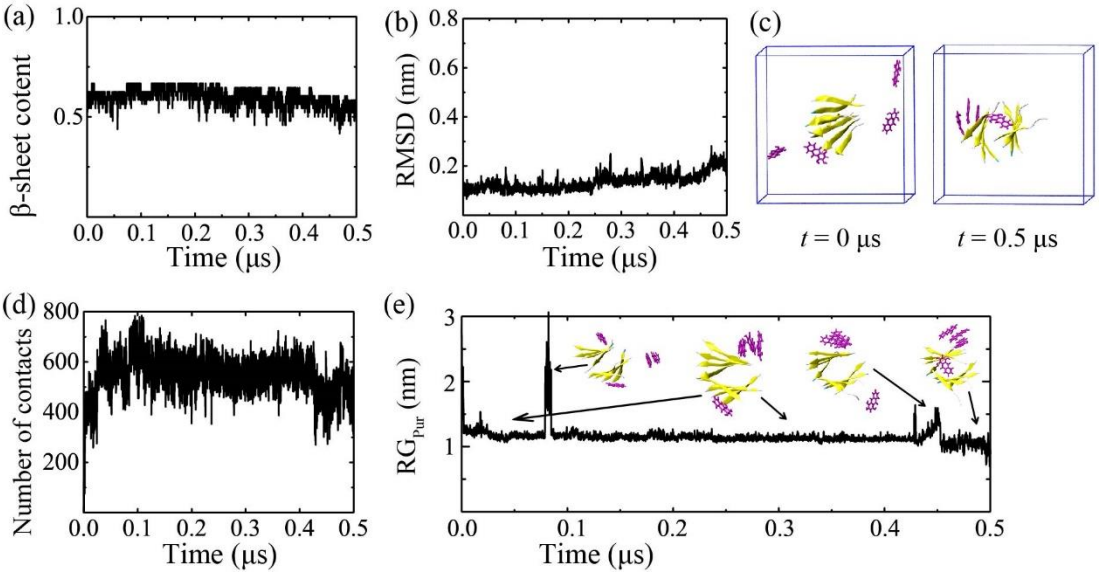

Fig. S3 (a) Time evolution of β-sheet content in the octamer-4Pur system. (b) Time evolution of Cα-RMSD relative to initial structure. (c) Snapshots of the initial and final structures. (d) Number of contacts between purpurin and octamer as a function of time. (e) Time evolution of RG for the four purpurins. Here, the equilibrated structure obtained from the final output of the protofibril octamer system, rather than the crystal structure, was used to model the octamer.