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

Supplementary: Interplay Between Hydrophobic Effect and Dipole Interactions in Peptide Aggregation at Interfaces†

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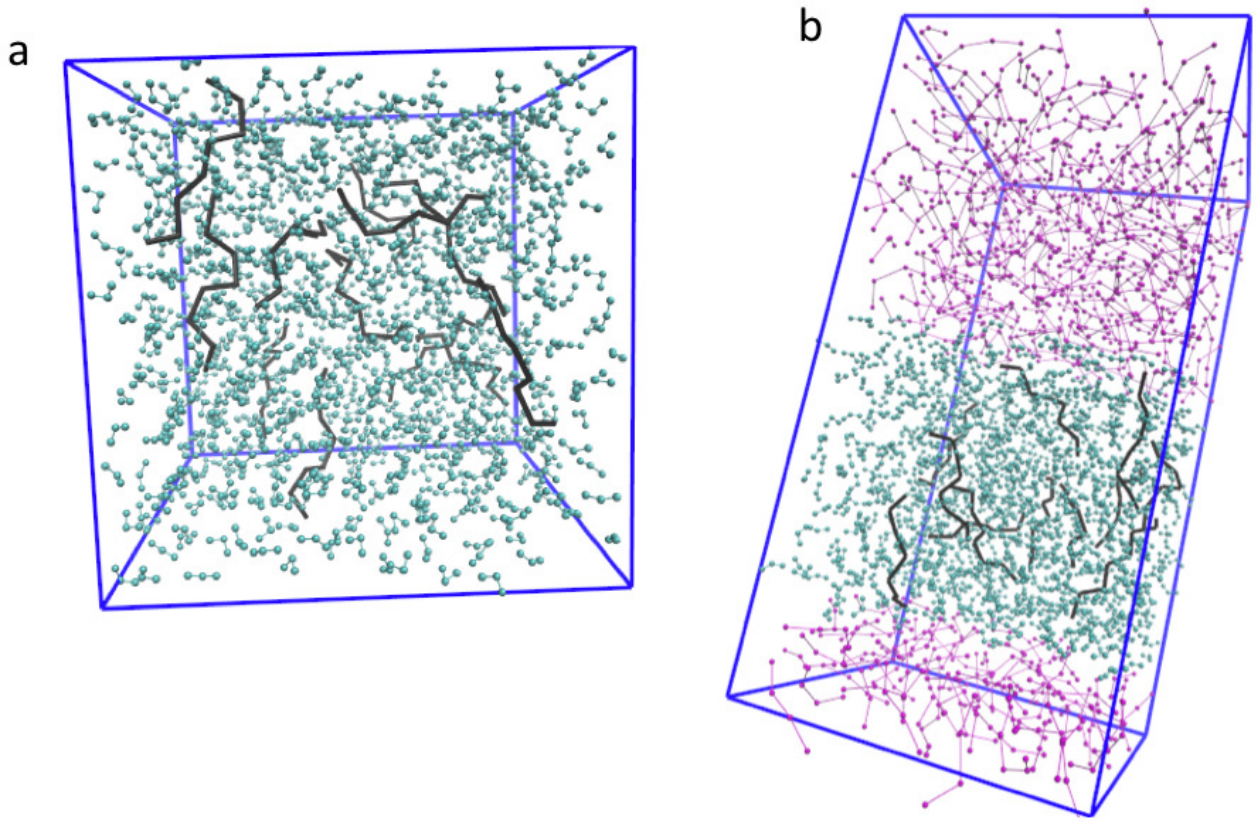

Fig. S1: Initial conformation of (a) system V in water and (b) system VI at water-hexadecane interface. Water is represented in cyan, hexadecane in purple, and peptide backbone in black.

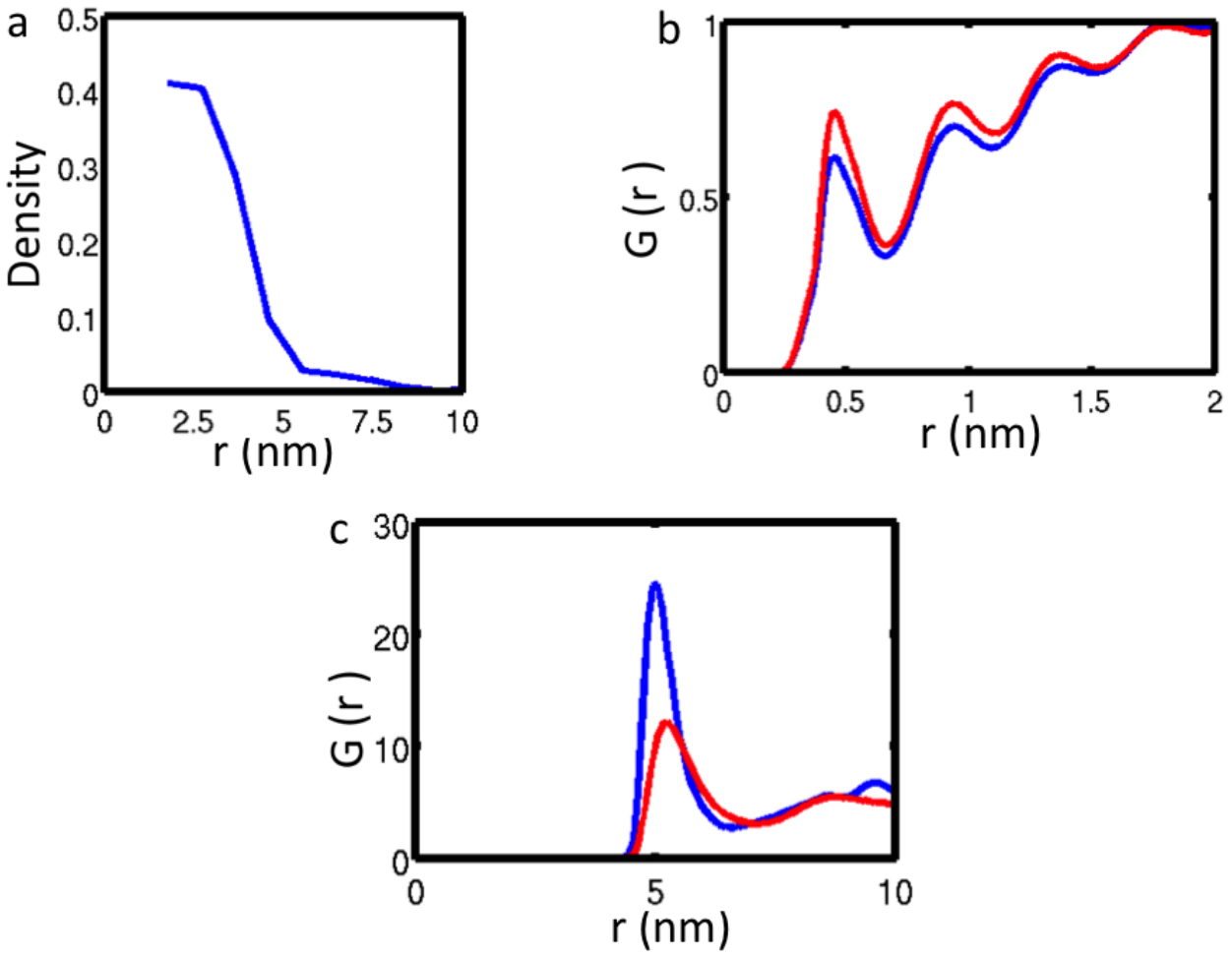

Fig. S2: (a) Pairwise distance distribution of positively and negatively charged dummy particles in helical and sheet conformations. (b) Radial distribution function evaluated between hydrophobic side chain and water beads of system V. Red and blue curves represent "fibril-like" and "cross-β" like conformations. (c) Pairwise distance distribution between backbone beads of adjacent peptides in an aggregate. Blue curve represents system V with dipolar particles, and red curve, system V without dipolar particles.

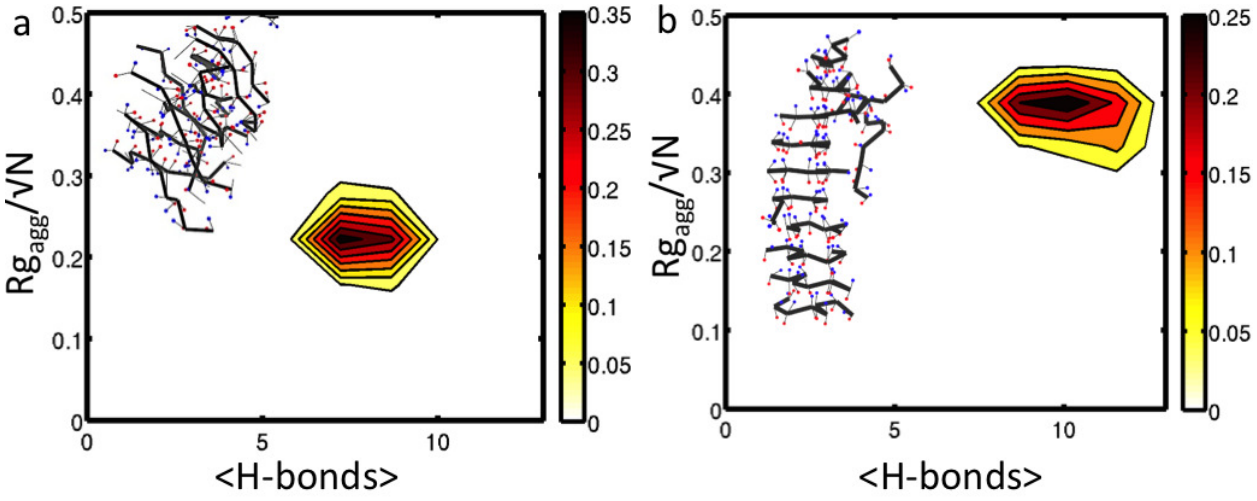

Fig. S3: Probability density plots using interpeptide pseudo H-bonds and radius of gyration of the aggregate over squareroot of N (number of monomers) as reaction coordinates for simulations exhibiting (a) "cross β" like and (b) "fibril-like" conformations in system V. Insets show representative conformations. Peptide backbone is shown in black, positive and negative dummies in blue and red, respectively.

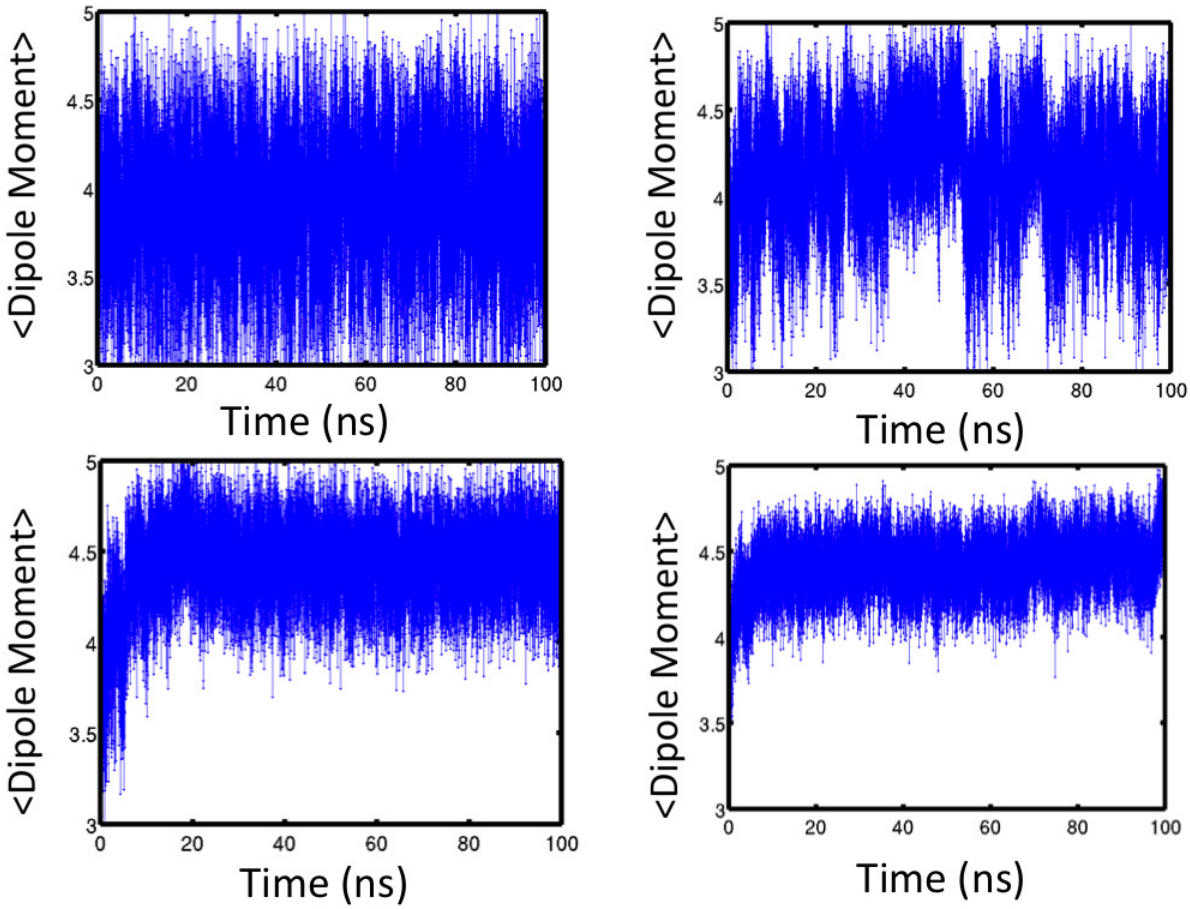

Fig. S4: Time evolution of average dipole moment per peptide backbone bead for (a) system I, (b) system II, (c) system III, and (d) system IV.

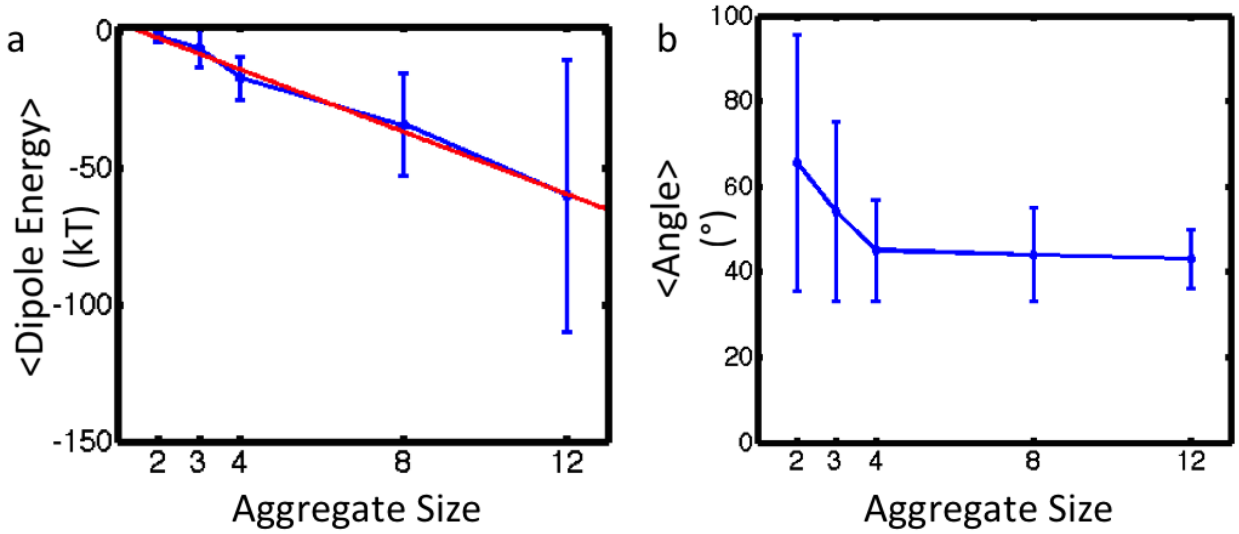

Fig. S5: (a) Dipole energy per peptide as a function of aggregate size, linear fit shown in red (b) Average angle between dipole moment vectors and the local electric field, with different aggregate sizes. All error bars represent 95% confidence interval.

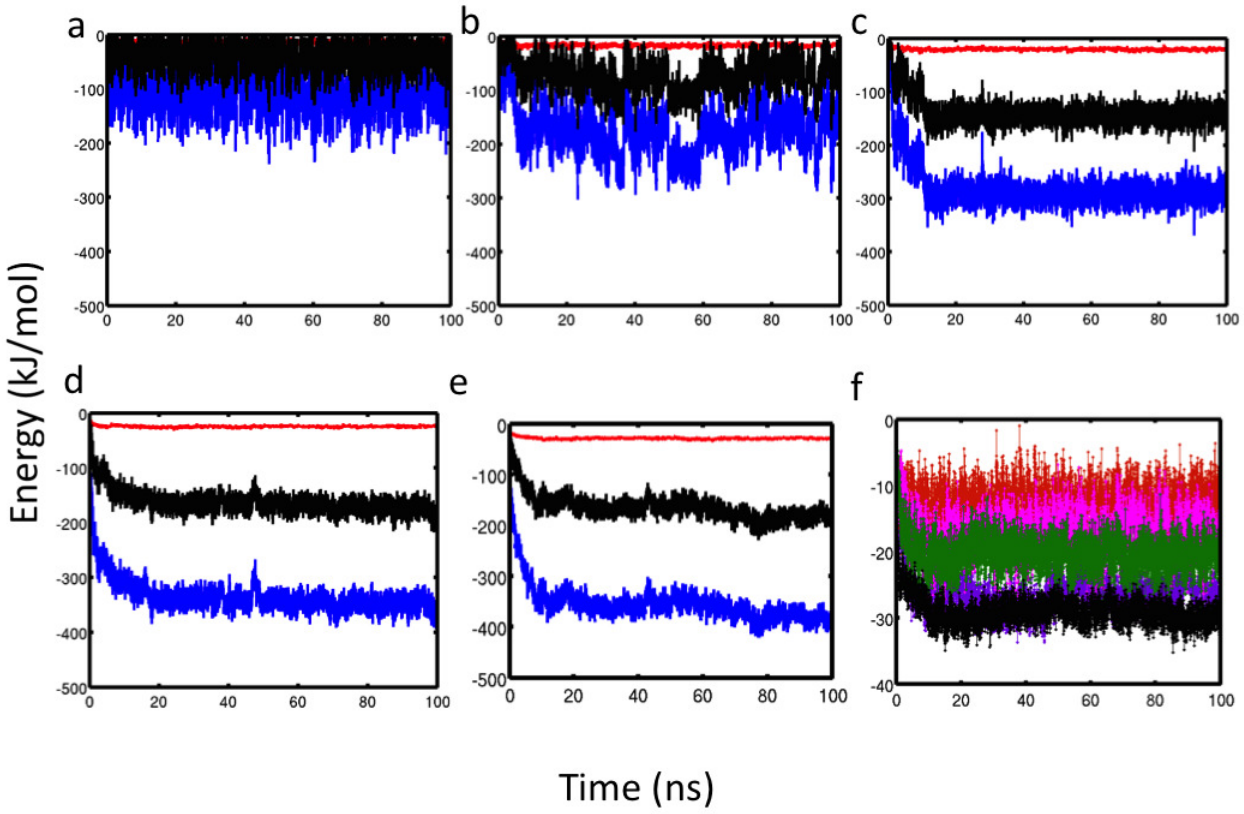

Fig. S6: Time evolution of the Lennard-Jones energy from hydrophobic side chain interactions (red), backbone Coulombic interaction (black) and total peptide-peptide energy (blue) for (a) 2 peptide , (b) 3 peptide, (c) 4 peptide, (d) 8 peptide, (e) 12 peptide system. (f) Hydrophobic side chain interactions of 2 (red), 3 (pink), 4 (green), 8 (purple) and 12 (black) peptide systems.Data obtained from one representative run, all energies are normalized by number of peptides in the aggregate.

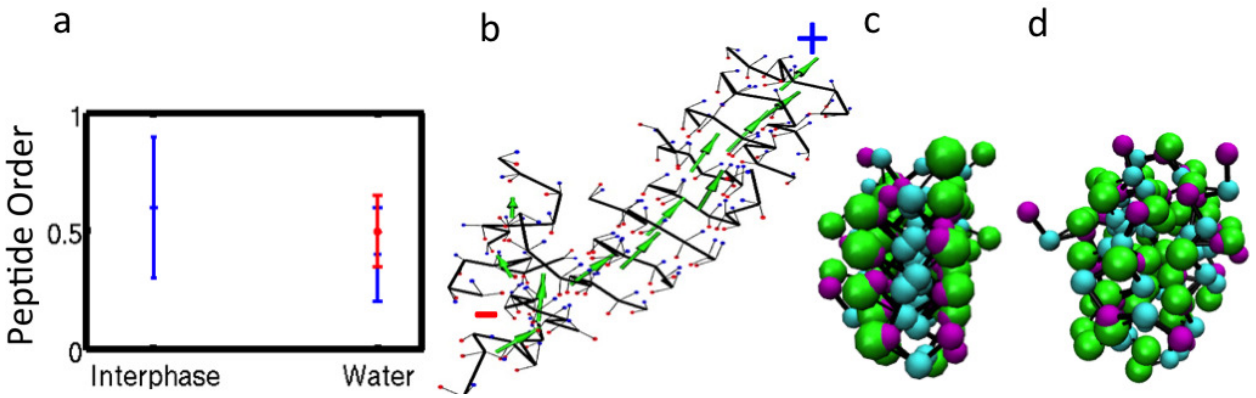

Fig. S7: (a) Average peptide order parameter of aggregates in system V and VI (blue), the "fibril-like" conformation seen in water is represented by the red points. All error bars represent 95% confidence interval for the mean (assuming normal distribution) of collective data, as standard error of the mean is negligible due to large number of conformational information collected. Representative conformation of fibril-like structure, (b) showing dipole alignment, (c) lateral view displaying hydrophobic bead alignment on either sides. Representative conformation of cross-β structure seen in system V, (d) lateral view displaying hydrophobic core. Green arrows in (b) represent dipole vectors of each peptide, red and blue represent negative and positive dummy particles. Backbone beads in (c) and (d) represented in cyan (hydrophobic residue) and purple (neutral residue). Hydrophobic side chain beads shown in green.

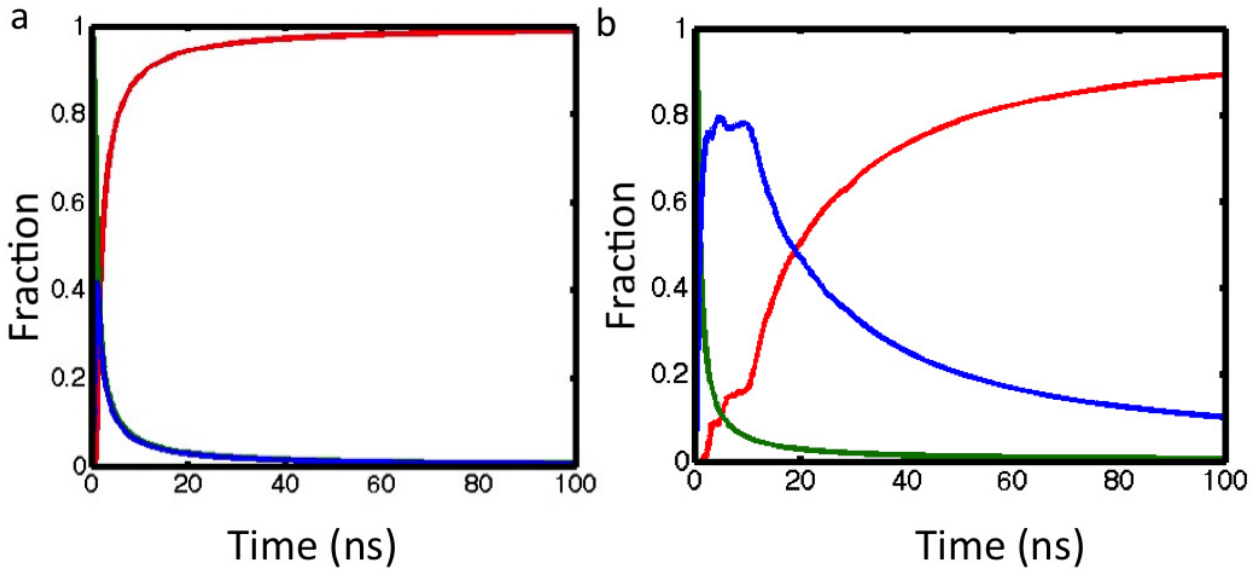

Fig. S8: Time evolution of the fraction of different species in (a) system VI and (b) system V. Green represents monomer fraction, blue, intermediate disordered fraction, and red, ordered aggregate conformation.

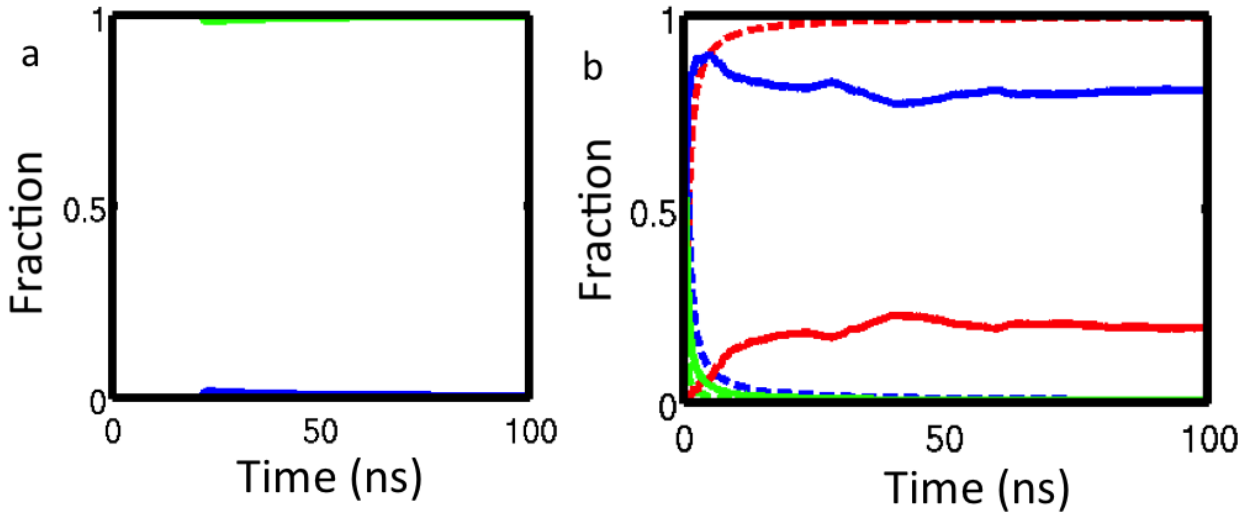

Fig. S9: Time evolution of the fraction of different species in (a) polyG octapeptides and (b) polyV octapeptides. Green represents monomer fraction, blue, intermediate disordered fraction, and red, ordered aggregate conformation.Dashed lines represent data at interfaces and solid lines, in water.

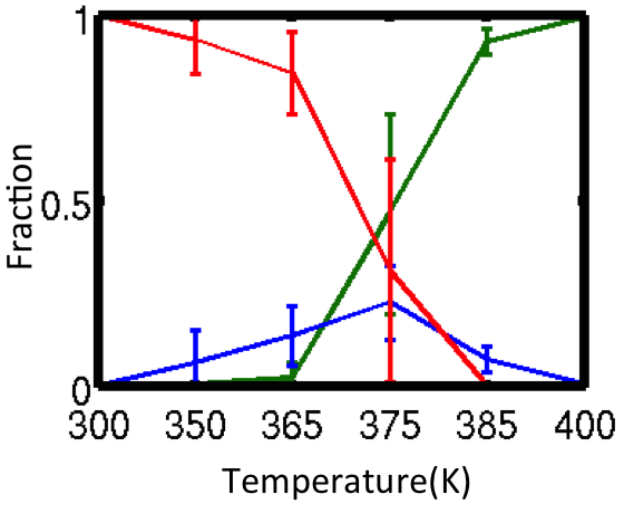

Fig. S10: Fraction of monomer (green curve), disordered aggregate (blue curve) and ordered aggregate (red curve) for system V. Data averaged over 8 runs for each temperature.

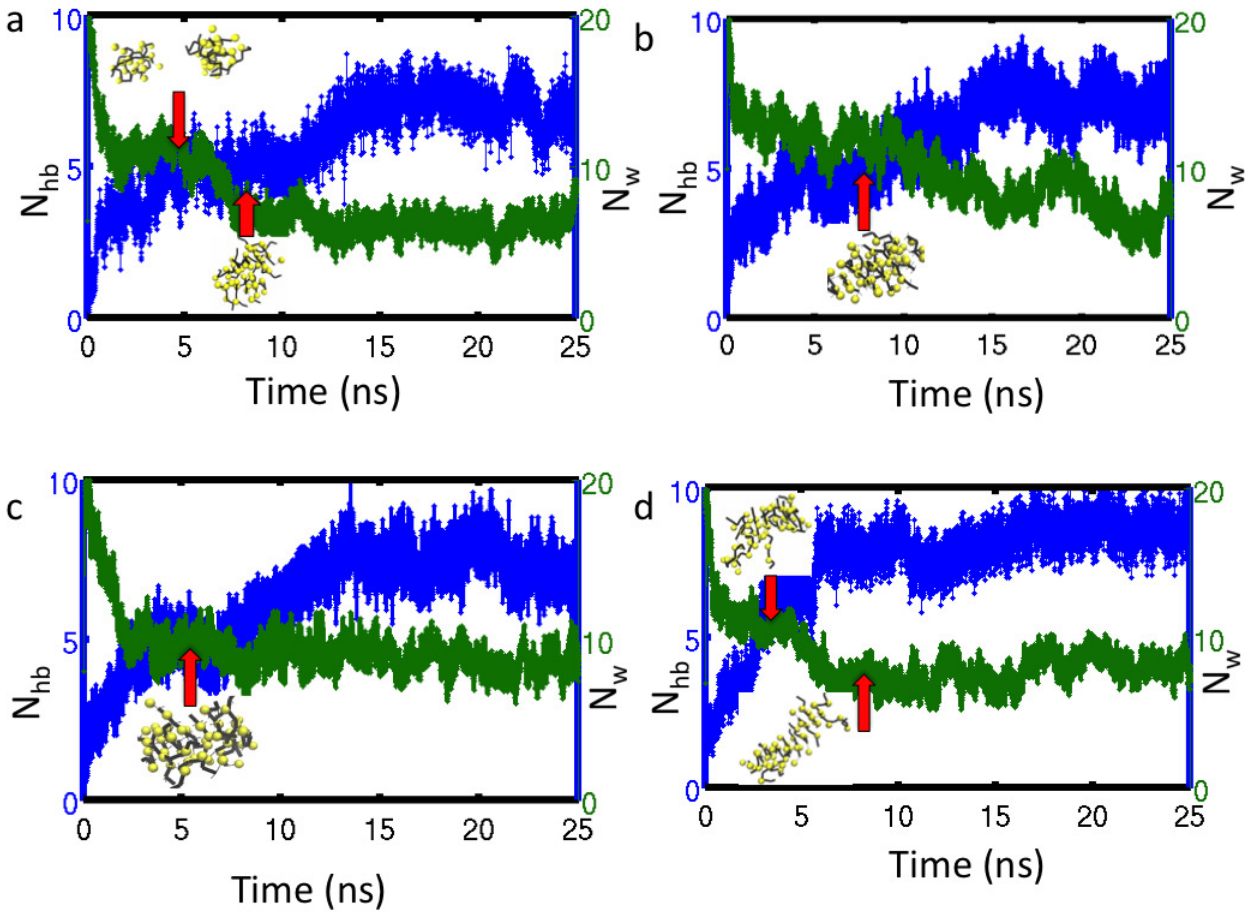

Fig. S11: Time evolution of the number of water molecules per peptide (N_w) in the first hydration shell of hydrophobic side chain beads (green), and the number of pseudo-interpeptide hydrogen bonds (N_{hb}) formed (blue). (a), (b), (c) and (d) represent four distinct and representative trajectories for system V. Typical conformations shown as insets, side chain beads represented in yellow and backbone beads in black.

1 Mechanisms of Water Expulsion

To better understand the significance of hydrophobic interactions in $(GV)_4$ octapeptide, we characterized the water expulsion from hydrophobic side chains in system V, as a distinct hydrophobic collapse is observed in systems IV and V. Figure S10 shows the time evolution of the number of water molecules per peptide, around the first hydration shell of hydrophobic side chain beads (N_w), and the number of interpeptide hydrogen bonds (N_{hb}), for a 12 peptide system.

In total, we observe four mechanisms of water expulsion: In 63.5% of the cases, as shown in Figure S10a, water expulsion is a single step process, followed by peptide reorganization, as described above. In this case two individual aggregates are formed initially within the first 2ns. These aggregates fuse to form one large aggregate by 7ns, after which N_w values remain constant. Similarly, a steep increase in N_{hb} is seen after 2ns, which further increases after the formation of the large aggregate at 7ns, indicating structural reorganization. Insets in Figure S10a, show the two initial aggregates and the larger aggregate, formed at 2ns and 7ns, respectively. In 12.5 % of the cases the expulsion of water is coupled with structural ordering (Figure S10b). That is, there is an increase in water expulsion (or decrease in N_w) with increase in pseudo H-bond content, with time. As the peptides collapse, there is simultaneous ordering. The inset of Figure S10b shows a representative partially ordered conformation. In 12.5% of the cases, N_w and N_{hb} are initially correlated, till 4ns, when N_{hb} continues to increase, while N_w remains constant (see Figure S10c). That is, within the first 4ns, increase in water expulsion (or decrease in N_w) is coupled with

increase in H-bond content, while after 4ns, the expulsion of water from the hydrophobic core is complete, but the number of H-bonds is still increasing, thus indicating structural ordering. The inset of Figure S10c shows a representative disordered, collapsed conformation at 5ns. In the case of the pathway that leads to a "fibril-like" conformation (12.5%) (Figure S10d), a small nucleus of ordered structure inside an aggregate is formed within 5ns (see first inset), as indicated by the initial drop in N_w while N_{hb} is still increasing. This nucleus precedes the ordering of other peptides in the aggregate. The second drop in N_w denotes further ordering of the peptides that results in a "fibril-like" conformation, as shown in the second inset of Figure S10d at 10ns. In this case, water expulsion from hydrophobic side chains is influenced by the interpeptide backbone dipole interactions.

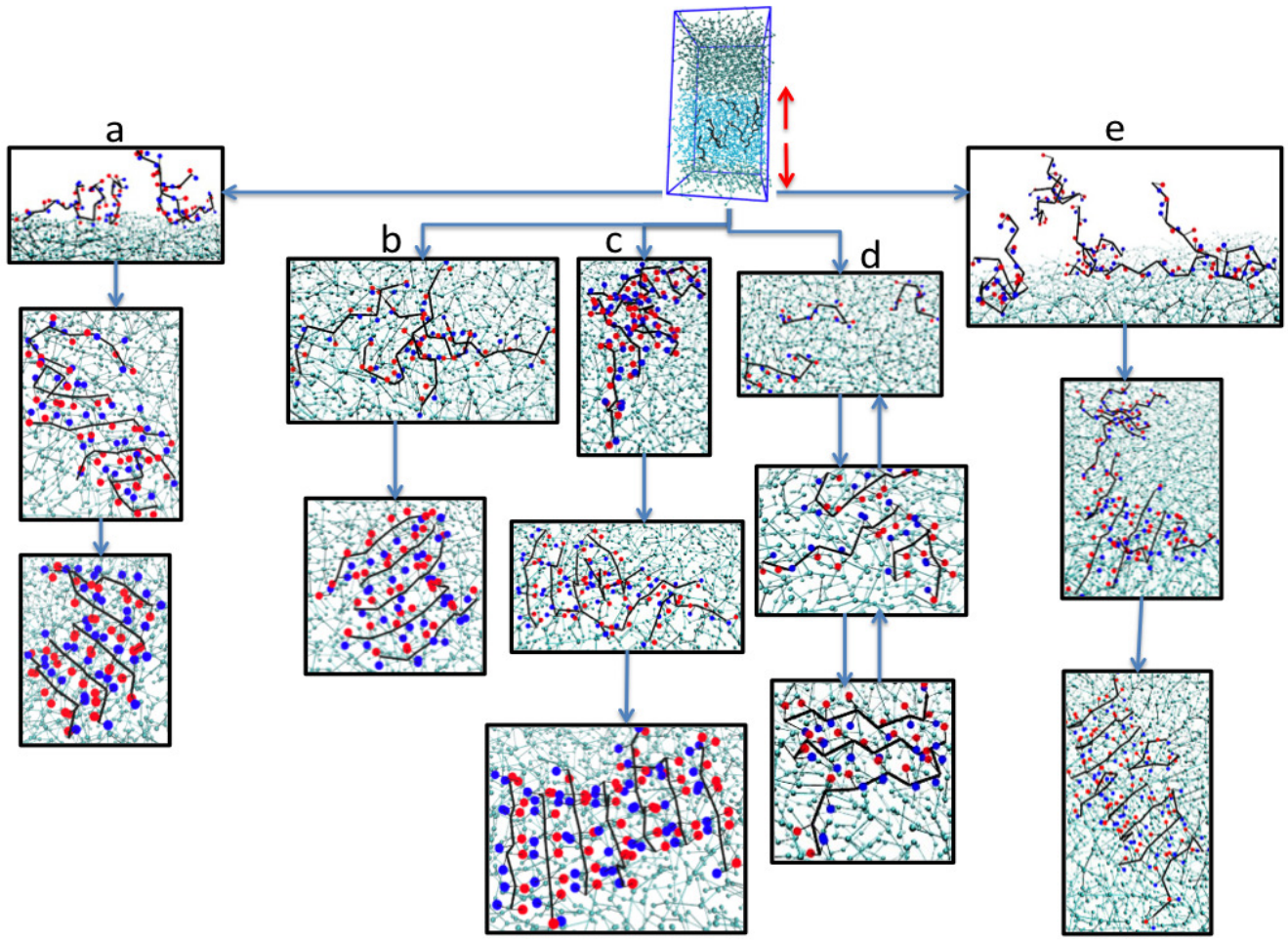

Fig. S12: Aggregation pathways observed in system VI, red arrows indicate that peptides aggregate at both interfaces; light blue represents water; black, the protein backbone; red and blue represent negative and positive dummy beads; and cyan represents hexadecane phase. (a), (b) ,(c) ,(d) and (e) represent five different mechanisms, see text for details.

2 Pathways of Peptide Aggregation on Hydrophobic Interface

Figure S12 details different mechanisms of surface mediated aggregation observed in system VI. We see 5 distinct pathways, of which 4 dominate or are more prevalent. Since there are two interfaces, the peptides get adsorbed to either. In mechanism (a), peptides adsorb to the surface individually, an ordered nucleus of 4 peptides is formed and the fifth peptide adds on to the ordered aggregate (fraction observed: 0.0625), in (b) the peptides adsorb to form a disordered aggregate on the surface, which rearranges to form ordered conformations (fraction observed: 0.1875). The third pathway (c) is the most common (fraction observed: 0.375), and is a condensation-ordering mechanism where, the peptides aggregate in water and then the aggregate gets adsorbed on the surface which realigns with time. Mechanism (d) is observed when three (or less) number of peptides get adsorbed to a surface (fraction observed: 0.1875). In this case, the aggregates are not stable, and can be ordered or disordered. Finally, in mechanism (e), peptides get adsorbed to the surface, form different aggregates (in this example, of size 4 and 5), which then fuse to form one ordered structure (fraction observed: 18.75). Also note, that some peptides can occasionally adopt a hairpin conformation in the aggregate.

References

1 D. Thirumalai, G. Reddy and J. E. Straub, *Acc. Chem. Res.*, 2011, **45**, 83–92.