

**Methylations of Tryptophan Modified Naphtoquinone Affect its Inhibitory Potential towards
A β Aggregation**

Supporting Information

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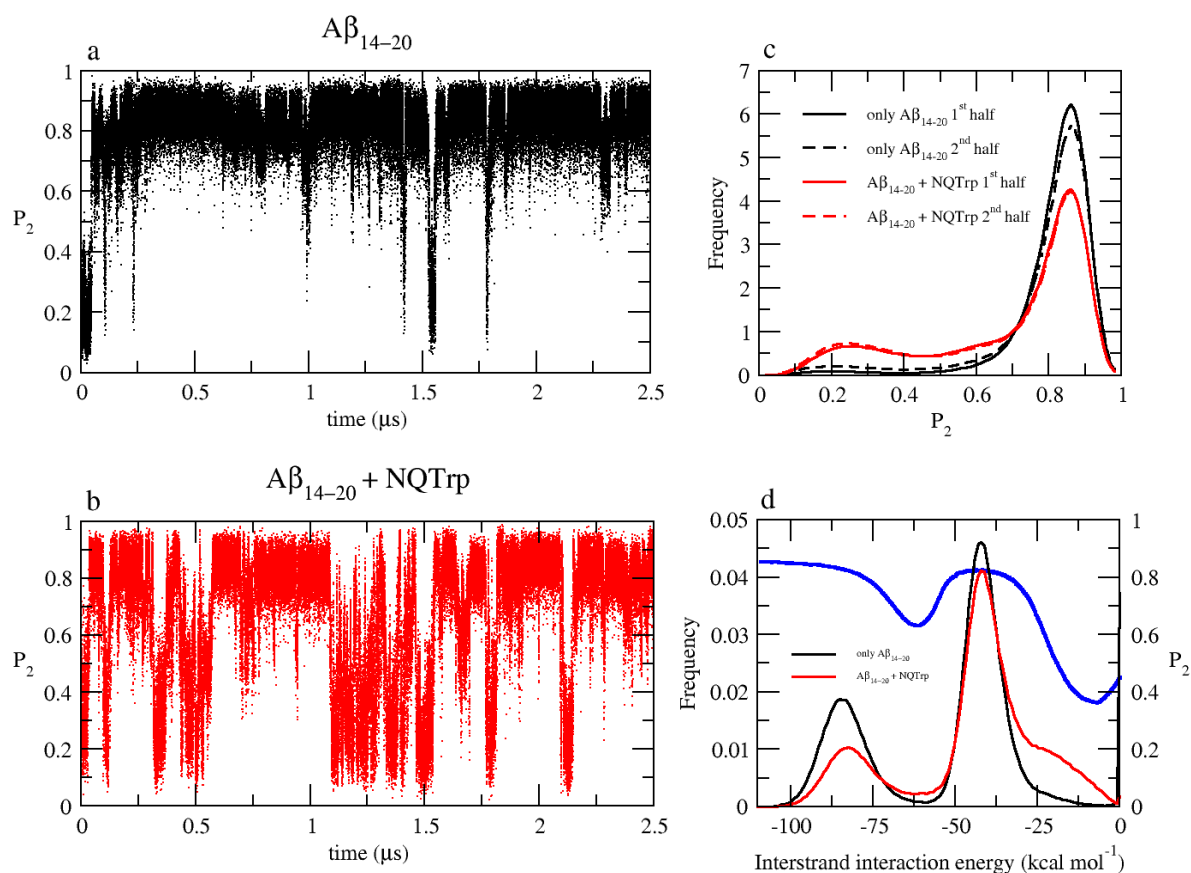


Figure S1. Analysis of the statistical significance of the distributions extracted from the MD sampling. (a) Time series of the nematic order parameter P_2 of free $A\beta_{14-20}$ trimeric system and (b) in presence of NQTrp. Several events of reversible formation of ordered aggregates are present already in a single 2.5- μs run. Similar time series are observed for the other nine runs. (c) Frequency histograms of the nematic order parameter P_2 for free $A\beta_{14-20}$ trimeric system (black curves) and in presence of NQTrp (red curves). Each curve represents a block average over half of the simulation data, i.e., five of the ten 2.5- μs runs. Since the deviations between pairs of blocks of data are much smaller than the differences between the simulations with and without NQTrp, one can safely conclude that the latter differences are not an artifact due to limited sampling. Converged sampling is observed also for the NQTrp inhibitors. (d) Distribution of the interaction energy of a single peptide with the remaining two peptides for $A\beta_{14-20}$ trimeric system in the absence (black line, left y-axis) and in the presence of NQTrp (red line, left y-axis), and average P_2 as a function of interaction energy (blue line, right y-axis). The two peaks of the energy distributions correspond to a peptide in the centre of an ordered oligomer (about -80 kcal/mol) and a peptide at the edge of an ordered oligomer (about -40 kcal/mol), as shown by cartoons in Figure 1b (inset of right panel) in the main text. The profile of P_2 shows that the two peaks of the interaction energy distribution correspond to high order (i.e., P_2 of about 0.8) while the remaining regions of the distribution to low order. In the presence of NQTrp, the frequency of the interstrand energy decreases in the peak regions while it grows in the latter regions.

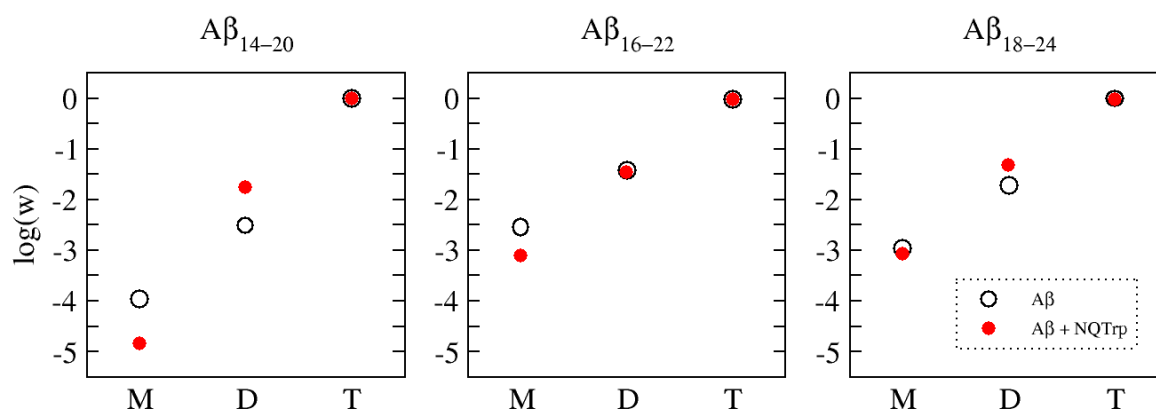


Figure S2. Probability of Aβ aggregation states. The data points show the logarithm of the statistical weight of monomers (M), dimers (D), and trimers (T) for the free Aβ systems (empty black circles) and in presence of NQTrp (filled red circles). The three states are defined according to the interaction energy between pairs of heptapeptides, e.g., the monomeric state has the three pairwise interaction energy values equal to zero. The presence of trimers is predominant in the three systems irrespectively of specific Aβ segment. This is due to the fact that these segments bracket the central hydrophobic core L₁₇VFFA₂₁ which has a strong propensity toward the aggregated state, and to the high concentration in the simulation box. The effect of NQTrp on the system is a small increment of the dimers, except for Aβ₁₆₋₂₂, and a reduction of the monomeric state. A very similar behavior is observed for all of the other compounds. This can be explained by the capability of polycyclic aromatic moieties to intercalate between aggregated Aβ peptides, establish an intermolecular hydrogen bond network, and, thus, destabilize the ordered structure of trimers without promoting full dissociation. The NQTrp derivatives influence the equilibrium properties of the oligomeric systems only marginally, nevertheless this effect is sufficient to produce a significantly decrease of ordered aggregation as observed in the simulations and experimentally.

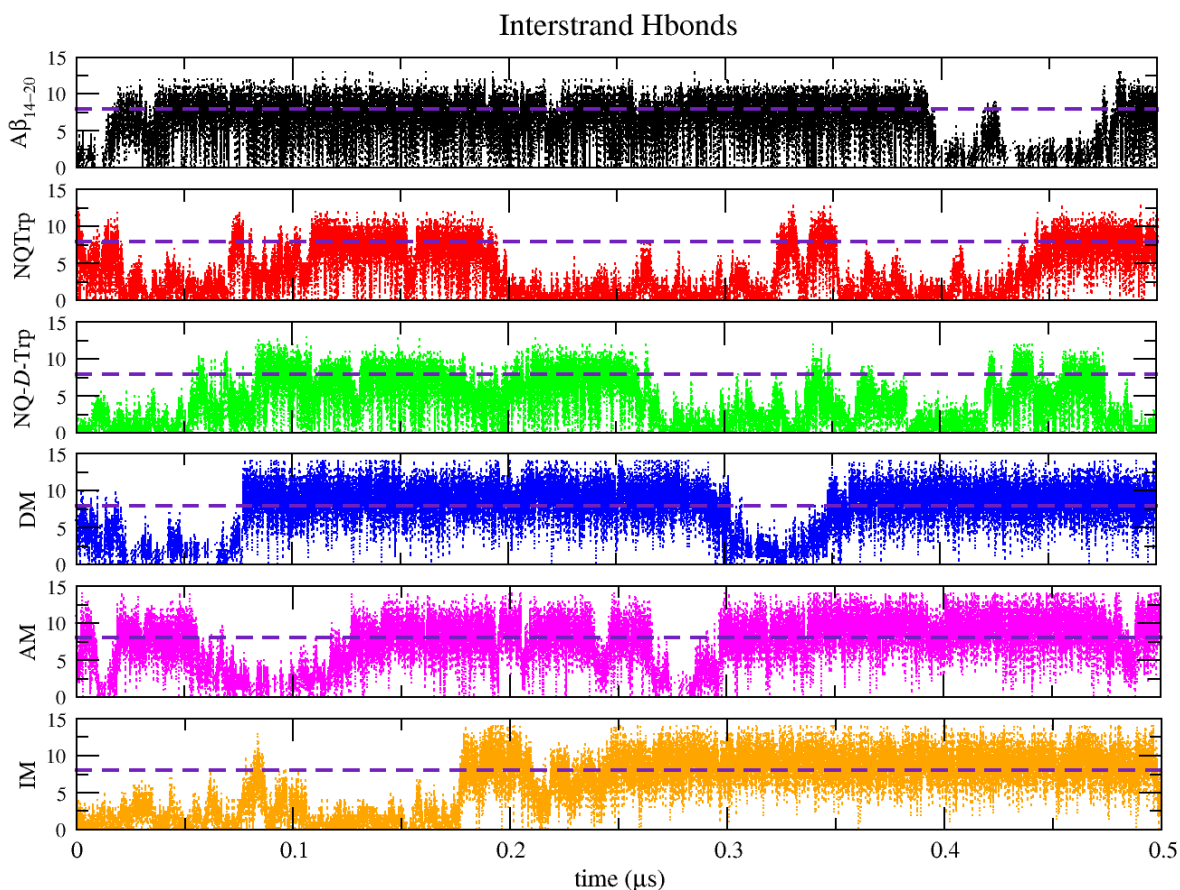


Figure S3. Time series of backbone interstrand hydrogen bonds (Hbonds). The backbone Hbonds are evaluated for only one of the three copies of $A\beta_{14-20}$. Thus the number of Hbonds can range from zero (isolated peptide or peptide associated through side chain contacts only) to 14 (central strand of the three-stranded β sheet). On average, the parent compound (NQTrp), NQ-*D*-Trp, and IM show a more pronounced reduction of backbone interstrand Hbonds than DM and AM. The first 0.5 μ s of a single 2.5- μ s run is shown, and a similar trend is observed in the remaining 2.0 μ s as well as in the other nine runs of each system. Note that the multiple events of association and dissociation observed already in 1/50th of the MD trajectories (0.5 μ s of a total of 10 x 2.5 μ s for each compound) indicate that the sampling is statistically significant. The horizontal dashed line at $y=8$ is drawn to better distinguish the ordered from the disordered aggregates.