Supporting Information for: Size-dependent Conformational Features of Aβ_{17-42} Protofilaments From Molecular Simulation Studies

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Supporting Texts:

1 Construction of The Minimum Free Energy Profile

The minimum free energy profile has been constructed by connecting those points of the free energy contour which represent the minima from all possible directions (in our case from two directions). The algorithm is based on the following steps

Step-1: The minimum value of the function with respect to the first variable (say λ_1) is searched keeping the second variable (say λ_2) constant.

Step-2: Keeping the λ_1 value as obtained from Step-1 fixed, the minimum value of the function with respect to λ_2 is searched.

Step-3: The searching process is repeated until the entire set of λ_1 and λ_2 values are sampled.

Step-4: The minimum free energy profile is constructed by connecting the minimum points obtained following above steps.

2 Effect of Charged State of The N-terminal Residue

In this study, we have performed MD simulations of five Aβ_{17-42} protofilaments in aqueous solution, where the terminal residues (Leu-17 and Ala-42) are taken as standard zwitterionic form to mimic the experimental neutral pH condition. Based on the results obtained from these simulations, we have proposed a probable growth mechanism of Aβ aggregates. Note that the protofilaments simulated in our case comprise of truncated Aβ peptide, where 16 N-terminal residues were absent. Thus, it is important to validate the observed results for the full-length protofilaments. However, one concern for such validation is the presence of charged N-terminal residues in these systems, which would remain uncharged in the full-length Aβ_{42} protofilaments. To examine whether the charged state of Leu-17 (the residue at the point of truncation) has any impact on the predicted growth mechanism, we have carried out two additional simulations by capping Leu-17, one with the lower order protofilament (O_5) and the other with the higher order protofilament (O_{12}). The N-terminal Leu-17 residue of each peptide in these two systems was capped with an acetyl group, while the C-terminus was kept in deprotonated form as carboxylate. We have followed the same protocols to simulate these two systems as described in Section 2.1 in the main manuscript.

We have constructed the minimum free energy profile as obtained from the free energy

contours of the two sytems as a function of two reaction coordinates, namely, the end-to-end distance (R_L) and the CTS twist angle (θ). The results are displayed in Figure S4. It is apparent from the figure that O_{12} exhibits two minimum energy conformations and their transformations occur due to rather small barrier height (within 1 kcal mol^{-1}) separating them. No such transition has been noticed for O_5, which is found to remain trapped within a single deep minimum separated from other minima by high energy barriers. The results are consistent with that obtained for the protofilaments with charged N-terminal residues, as discussed in the article (see Figure 6). Thus, it is clear that the minimum free energy profiles of truncated Aβ_{17-42} protofilaments is independent of the charged state of the N-terminal residue. Therefore, we believe that the amyloid growth mechanism as suggested from our analysis of Aβ_{17-42} protofilaments should be valid for the full-length Aβ_{42} peptides.

Supporting Tables:

Table S1: The Average Values of RMSD ($\langle RMSD \rangle$) as Obtained for the Two Terminal and Central Peptide Monomers in Different Aβ Protofilaments. The Values in the Parentheses are the Standard Deviations.

	$\langle RMSD \rangle$ (Å)		
protofilament	TERM-1	CENTER	TERM-2
O_5	8.00 (0.29)	4.21 (0.18)	4.34 (0.24)
O_8	4.18 (0.25)	3.21 (0.15)	4.17 (0.41)
O_{10}	9.47 (0.25)	5.41 (0.49)	8.62 (0.58)
O_{12}	6.15 (0.44)	4.44 (0.25)	4.45 (0.35)
O_{14}	9.42 (0.22)	2.25 (0.14)	6.07 (0.62)

Table S2: Total Number of Trimeric Units Considered for the Calculation of Binding Free Energies for the Selected Conformational States of the Aβ Protofilaments.

protofilament	I	II	III	IV	V
O_5	1722	11184	1734	–	–
O_8	1644	13704	1596	–	–
O_{10}	1224	6520	2750	8960	1048
O_{12}	1490	14880	2750	11220	1430
O_{14}	1608	6528	4512	16404	1704

Table S3: Binding Free Energies and the Corresponding Components (in kcal mol^{-1}) for the Selected Conformational States of the Aβ Protofilaments as Obtained from Trajectories with Modified Initial Configurations of the Protofilaments. The Values in the Parentheses are the Standard Deviations.

protofilament	state	ΔG_{vdw}	ΔG_{elec}	ΔG_{GB}	ΔG_{nps}	ΔG_{MM}	ΔG_{sol}	$T\Delta S$	ΔG_{bind}
	I	-87.99	-86.52	100.12	-26.62	-174.51	73.50	-294.42	193.41
		(10.95)	(1.77)	(1.30)	(0.14)	(11.42)	(1.27)		
O_5	II	-108.42	-84.67	101.27	-26.50	-193.09	74.77	-107.26	-11.06
		(2.26)	(0.37)	(0.30)	(0.03)	(2.29)	(0.29)		
	III	-109.94	-95.16	113.04	-27.55	-205.10	85.49	-268.85	149.24
		(9.84)	(2.11)	(1.79)	(0.13)	(10.06)	(1.74)		
	I	-168.07	-21.68	30.63	-26.11	-189.75	4.52	-347.23	162.00
		(0.70)	(1.94)	(1.66)	(0.10)	(2.29)	(1.63)		
O_8	II	-166.49	-33.11	43.20	-26.00	-199.60	17.20	-92.48	-89.92
		(0.19)	(0.50)	(0.45)	(0.03)	(0.53)	(0.46)		
	III	-164.91	-54.84	66.09	-25.87	-219.75	40.22	-324.73	145.20
		(0.73)	(1.64)	(1.55)	(0.10)	(1.58)	(1.58)		
	I	-60.29	-36.60	50.04	-26.69	-96.89	23.35	-329.45	255.91
		(4.58)	(1.20)	(1.68)	(0.08)	(5.97)	(2.72)		
	II	-90.68	-38.06	47.32	-26.33	-128.74	20.99	-94.58	-13.17
		(2.18)	(0.78)	(0.39)	(0.04)	(3.04)	(1.41)		
O_{10}	III	-108.54	-34.63	41.05	-25.71	-143.17	15.34	-200.35	72.52
		(2.91)	(1.78)	(1.11)	(0.09)	(3.36)	(2.12)		
	IV	-138.05	-44.53	49.45	-25.44	-182.58	24.01	-90.22	-68.35
		(1.21)	(0.65)	(0.46)	(0.03)	(1.41)	(0.47)		
	V	-126.51	-44.34	49.84	-25.36	-170.85	24.48	-299.04	152.67
		(3.94)	(2.28)	(1.81)	(0.13)	(4.73)	(1.89)		
	I	-167.27	-32.84	42.72	-26.26	-200.11	16.46	-328.25	144.60
		(0.76)	(2.47)	(2.23)	(0.10)	(2.65)	(2.22)		
	II	-161.09	-37.50	40.79	-25.32	-198.59	15.47	-79.95	-103.17
		(0.17)	(0.60)	(0.51)	(0.03)	(0.65)	(0.51)		
O_{12}	III	-168.02	-29.30	38.54	-26.35	-197.32	12.19	-195.07	9.94
		(1.10)	(2.92)	(1.68)	(0.10)	(3.23)	(1.67)		
	IV	-161.37	-36.43	47.50	-25.41	-197.80	22.09	-119.75	-55.96
		(0.22)	(0.73)	(0.62)	(0.03)	(0.80)	(0.61)		
	V	-161.11	-27.13	37.49	-25.44	-188.24	12.05	-311.97	135.78
		(0.75)	(2.20)	(1.68)	(0.09)	(2.55)	(1.66)		
	I	-164.09	-34.33	41.20	-26.12	-198.42	15.08	-317.89	134.55
		(0.71)	(1.48)	(1.12)	(0.10)	(1.89)	(1.09)		
	II	-163.95	-39.25	43.06	-26.23	-203.20	16.83	-98.09	-88.28
		(0.34)	(0.55)	(0.46)	(0.05)	(0.69)	(0.45)		
O_{14}	III	-164.00	-43.95	47.76	-26.20	-207.95	21.56	-134.43	-51.96
		(0.42)	(0.82)	(0.71)	(0.06)	(0.98)	(0.69)		
	IV	-165.24	-56.13	47.91	-26.40	-221.37	21.51	-82.19	-117.67
		(0.16)	(0.43)	(0.37)	(0.02)	(0.50)	(0.36)		
	V	-172.22	-44.88	53.96	-27.47	-217.10	26.49	-358.09	167.48
		(0.73)	(2.19)	(1.72)	(0.11)	(2.21)	(1.74)		

Supporting Figures:

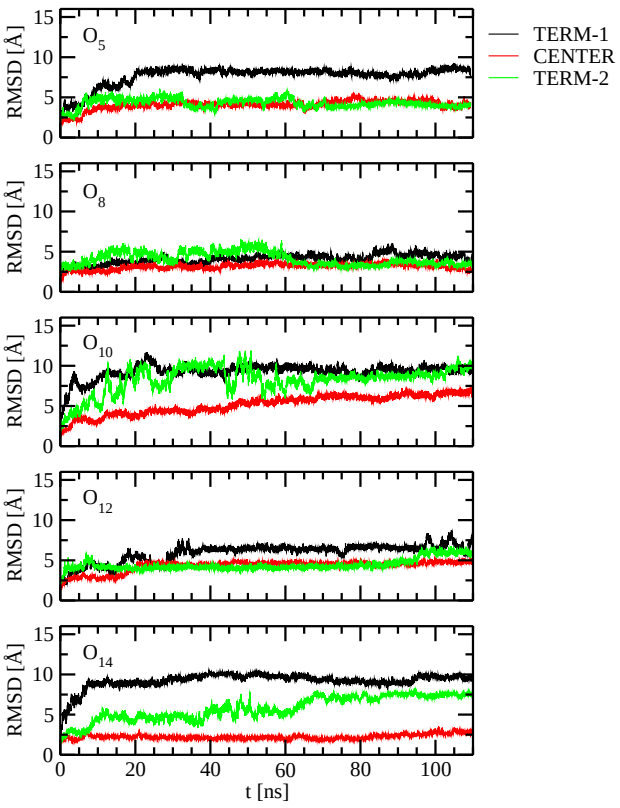

Figure S1: Time evolutions of the RMSDs of the two terminal and the central Aβ peptide monomers in different protofilaments. The calculations are carried out with respect to the corresponding initial structures.

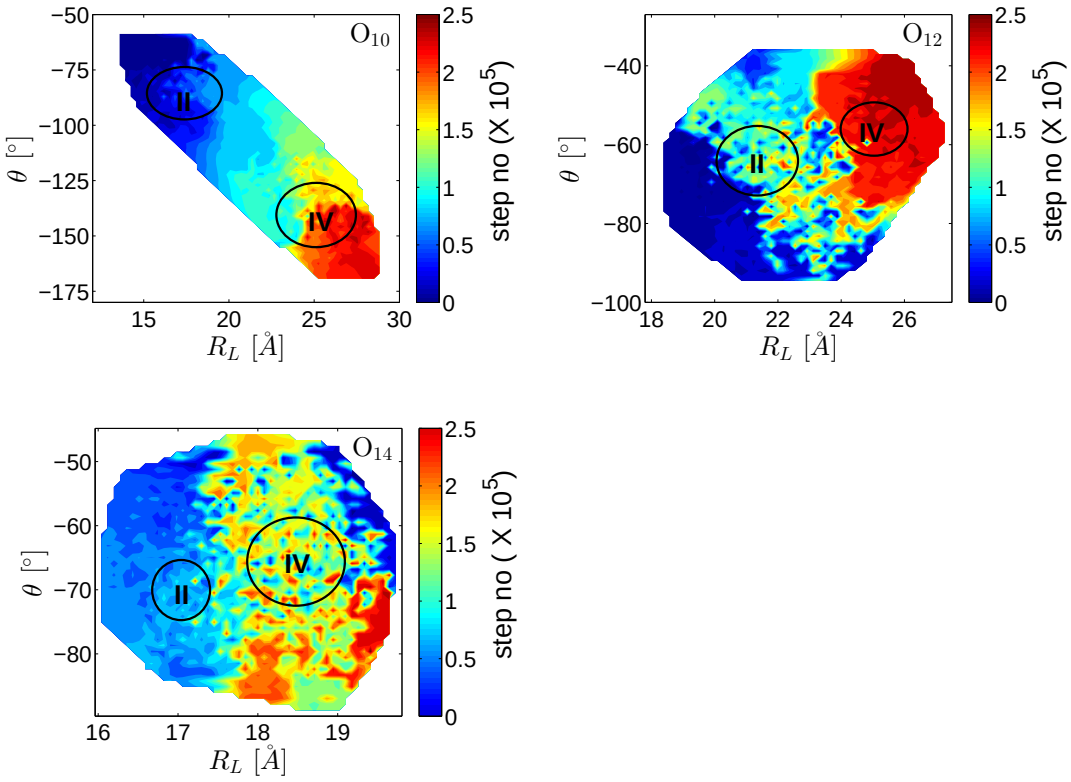

Figure S2: Time evolution of the two-dimensional free energy contours of O_{10}, O_{12}, and O_{14}. The peptide end-to-end distance (R_L), the CTS twist angle (θ), and the simulation step numbers are plotted along the x-, y-, and z-axes, respectively. The two most stable states for each protofilament are circled for visual clarity.

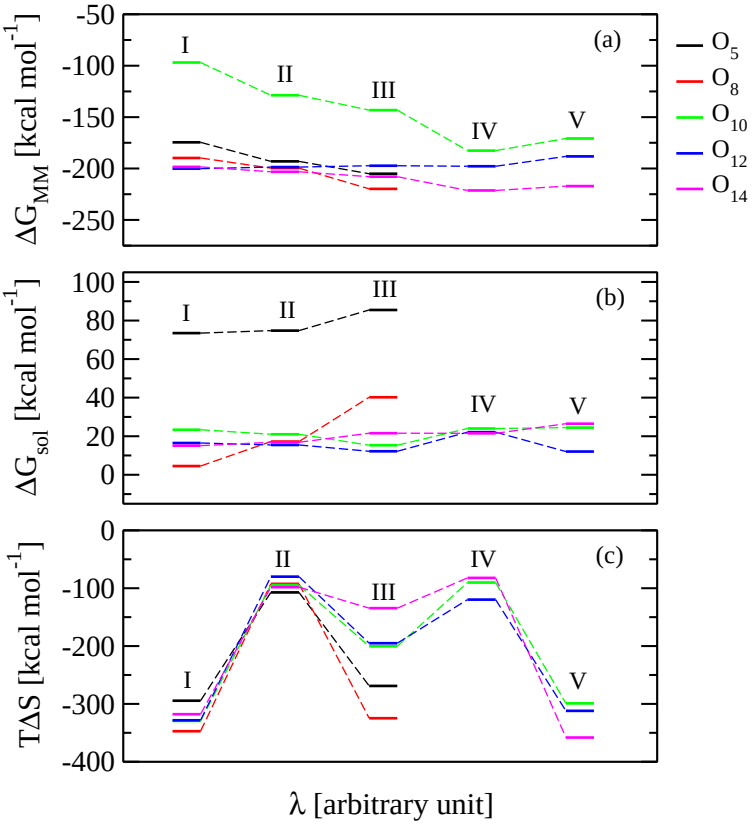

Figure S3: Contributions of different components of ΔG_{bind}, namely, (a) the intermolecular interaction energy (ΔG_{MM}), (b) solvation free energy (ΔG_{sol}), and (c) entropy contribution on complexation ($T\Delta S$) for the selected conformational states I to V (see Figure 6(b) of the main text) of different Aβ protofilaments as obtained from the second set of trajectories.

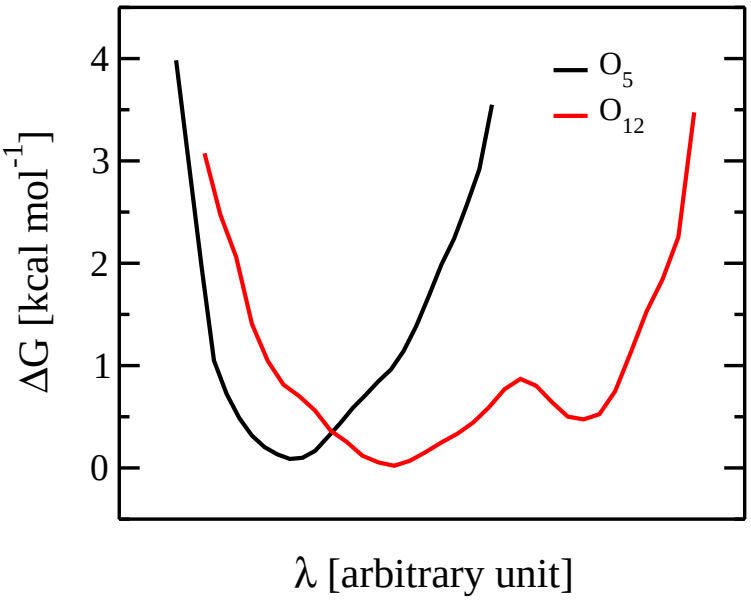

Figure S4: The free energy profiles (ΔG) along the minimum energy pathways for the Aβ protofilaments O_5 and O_{12} with capped N-terminal residues of the individual peptides.