Supplementary Information for

Molecular Mechanism of Misfolding and Aggregation of Aβ(13-23)

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Table S1. RSMIP of the 10 largest eigenvectors of the three simulations (simI-III) at different intervals of the trajectories.

Simulation pair	Trajectory interval			
	0-50 ns	50-100 ns	100-150 ns	150-200 ns
SimI - SimII	0.7589	0.7363	0.7248	0.6656
SimII - SimIII	0.7698	0.7702	0.7973	0.7212
SimI - SimIII	0.7859	0.7757	0.7835	0.7509

Supplementary Figures

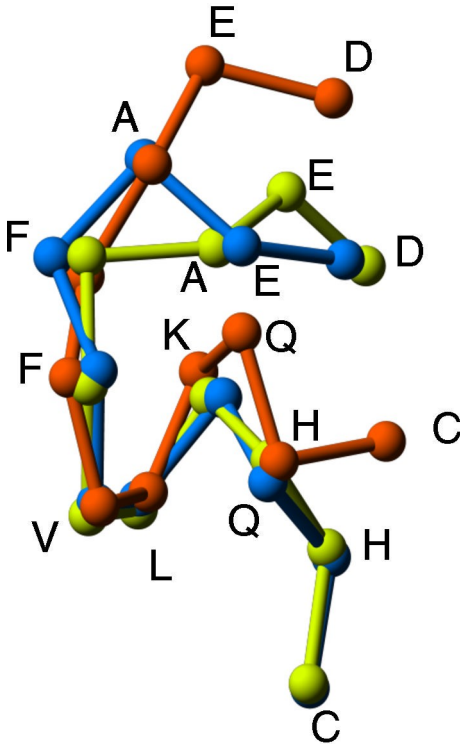

Figure S1. Overlaid representative Cα trace structure of the largest cluster of simulation I, II and III. Blue, simulation I; Red, simulation II; Green, simulation III.

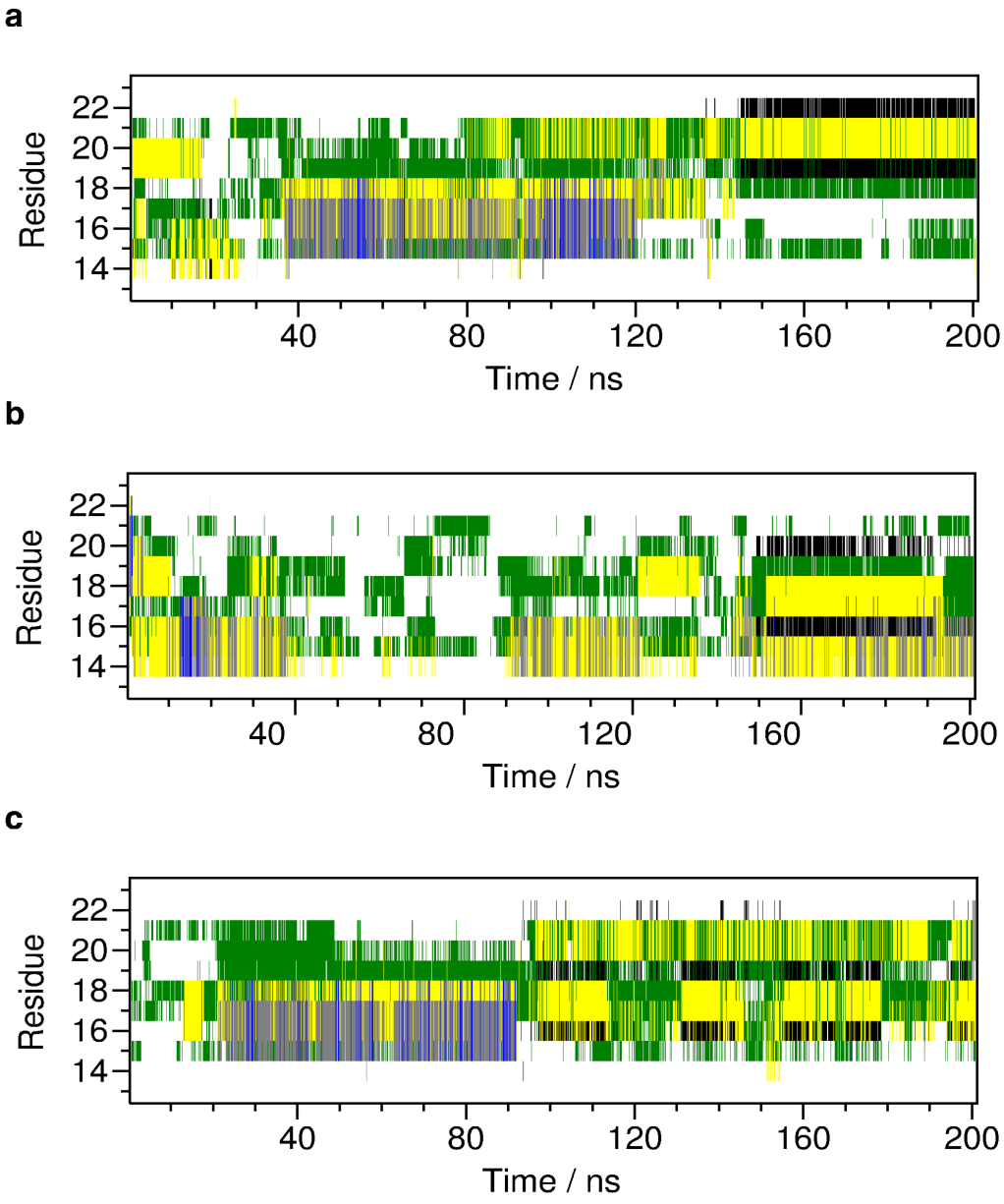

Figure S2. DSSP analysis of the trajectories of simulations I-III of Ac-[Cys^{13}]Aβ(13-23)-NH_2. (**a**) simI. (**b**) simII. (**c**) simIII. Random meander is white, β-bridge is black, β-bend is green, β-turn is yellow, α-helix blue and 3_{10}-helix is gray.

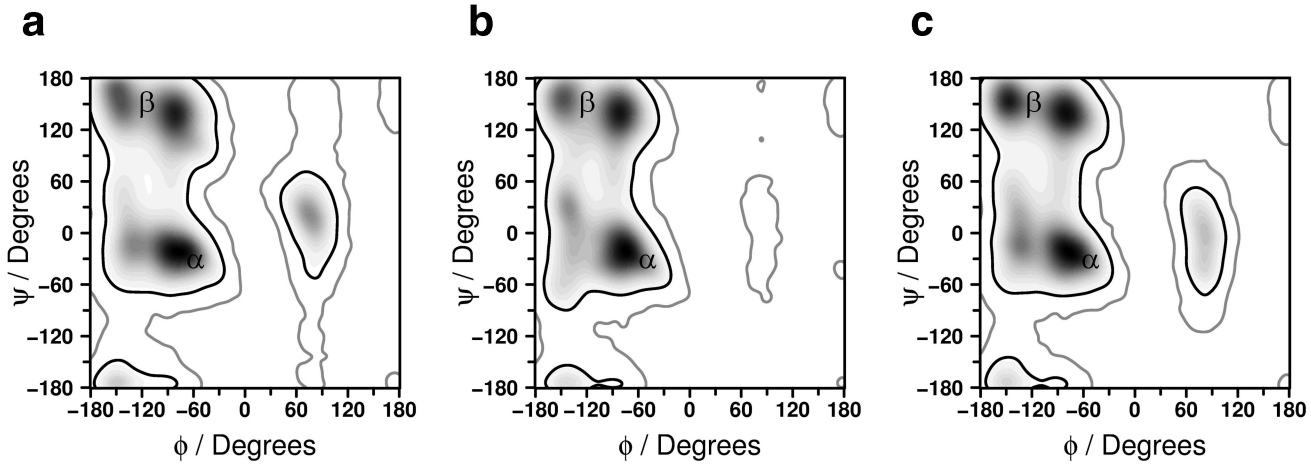

Figure S3. Ramachandran plot for simulations I-III. (**a**) simI. (**b**) simII. (**c**) simIII. The dark regions indicate the conformation explored during simulations. α-helix and β-sheet conformations are labeled. Gray line indicates allowed (99.95% contour level) and black line indicates favored (98% contour level) region of conformational space[1].

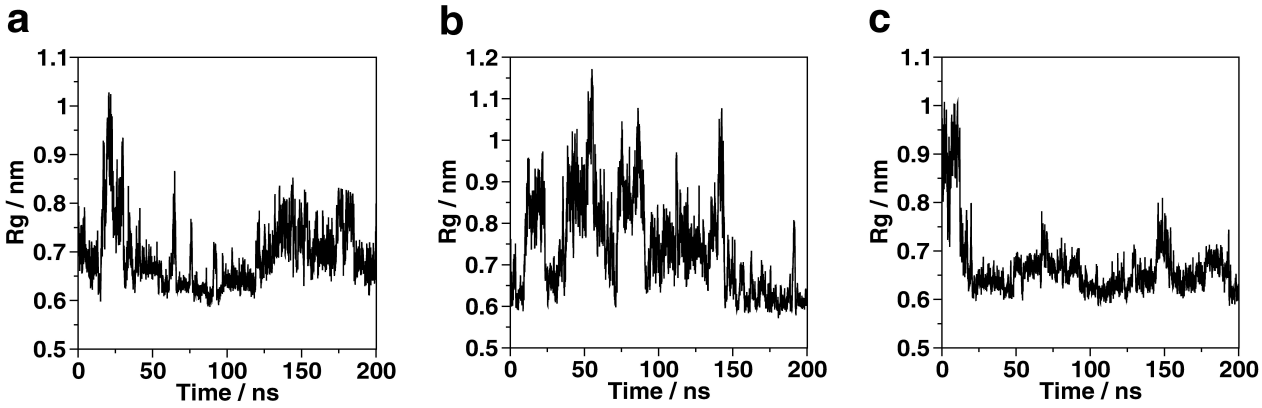

Figure S4. The radius of gyration (Rg) of the peptide in simulations I-III. (**a**) simI. (**b**) simII. (**c**) simIII.

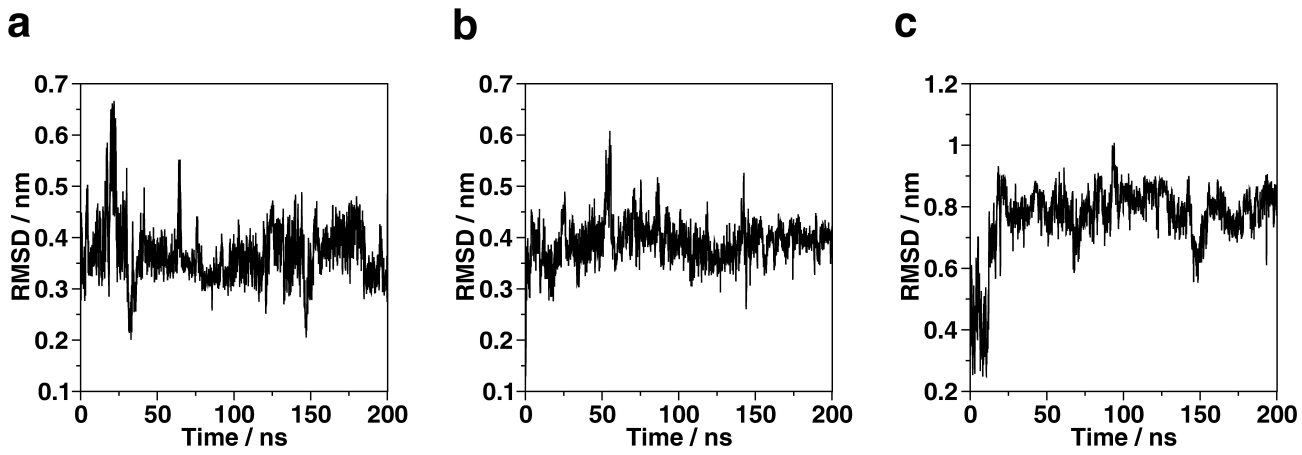

Figure S5. The RMSD of the backbone of atoms in simulations I-III. **a**) simI. (**b**) simII. (**c**) simIII.

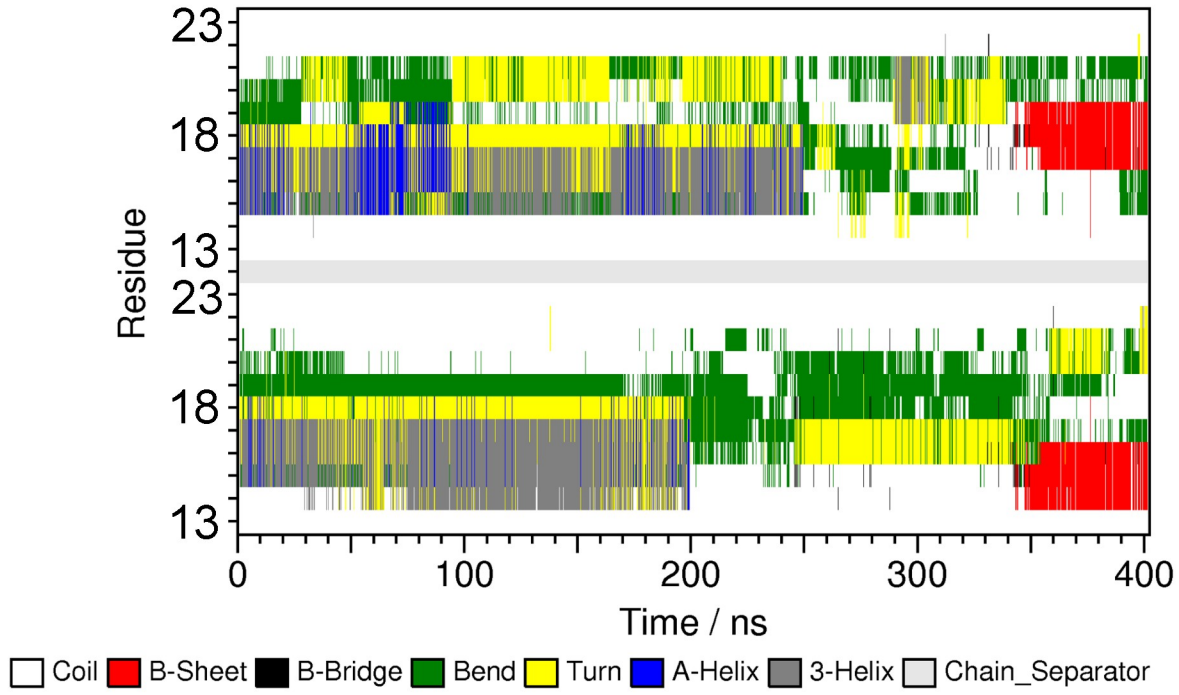

Figure S6. DSSP analysis of 400 ns trajectory of the dimer simulation. Bottom panel, chain A; top panel, chain B. White is coil, black is bridge, green is bend, yellow is β-turn, blue is α-helix, gray is 3_{10} helix and red is β-sheet. The two chains are separated by a light gray ribbon.

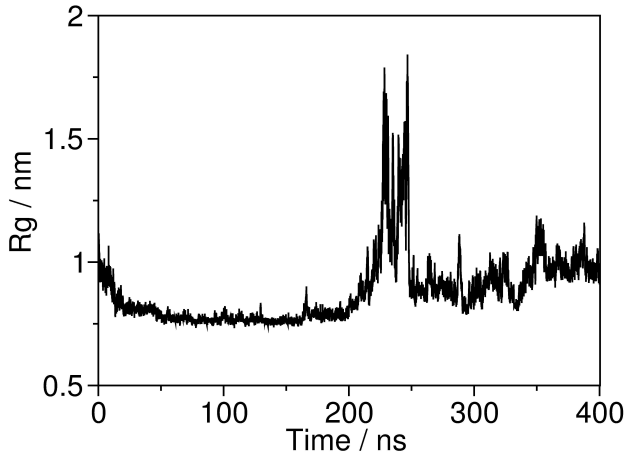

Figure S7. The radius of gyration (Rg) of the dimer during the 400 ns simulation.

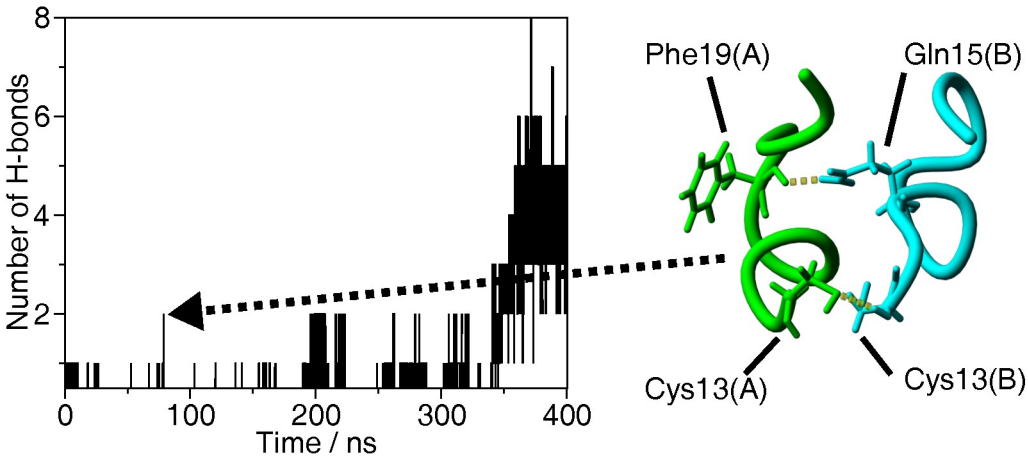

Figure S8. Number of hydrogen bonds during MD simulation of the dimer structure. The inserted structure shows H-bonds between the two Cys residues and between the amide H of Phe^{19} of chain A and the side chain of Gln^{15} of chain B.

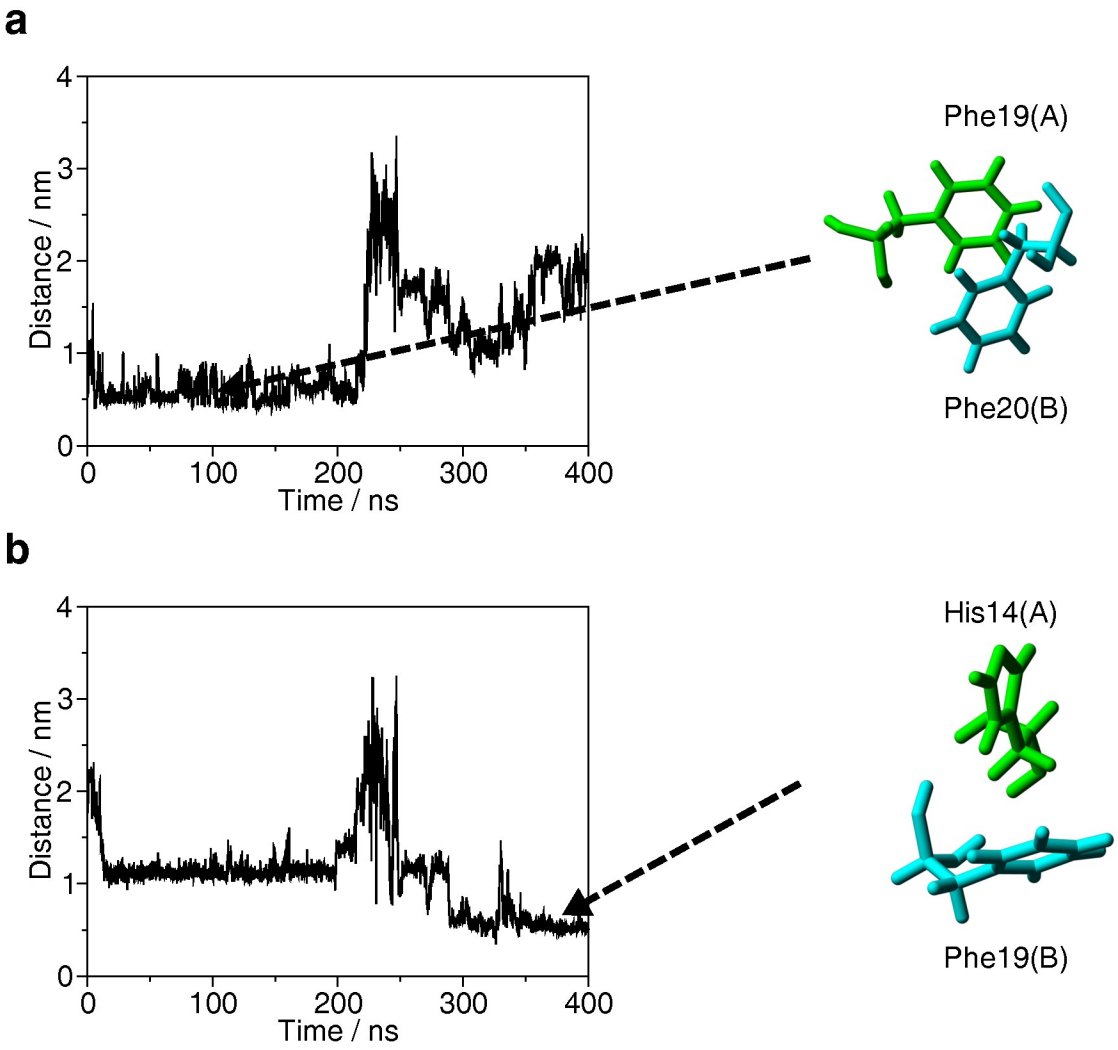

Figure S9. The weakly polar interactions during MD simulation of the dimer structure. (**a**) the distance of Phe^{19} of chain A and Phe^{20} of chain B. (**b**) the distance between $C^{\beta}H$ of His^{14} of chain A and Phe^{19} of chain B. On the left side of the figure snapshots from the trajectory illustrate the interactions.

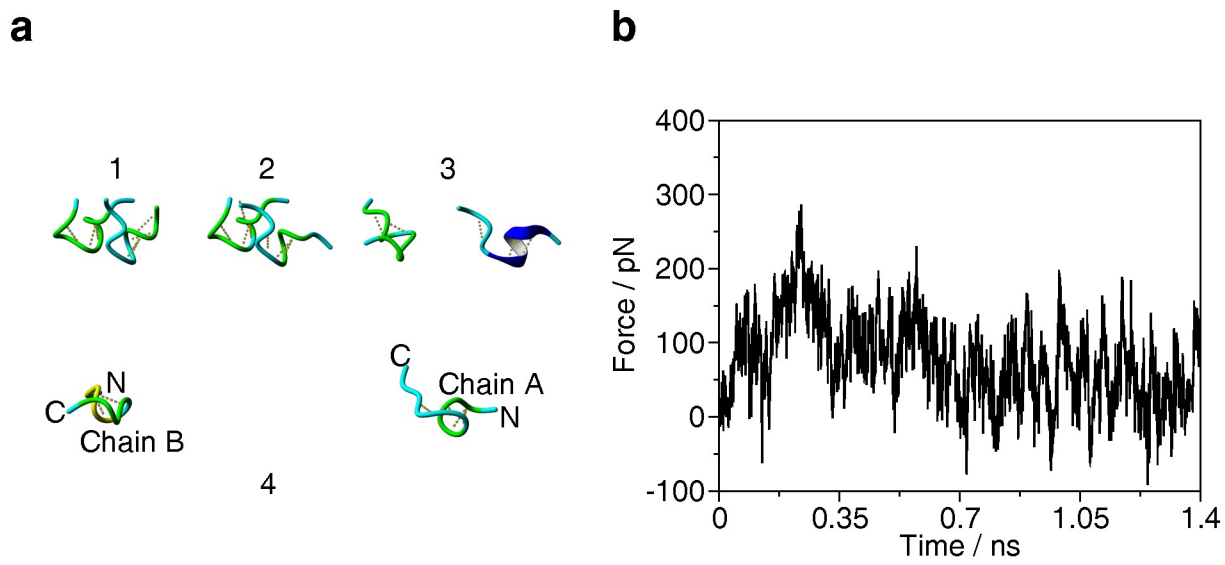

Figure S10. Force-induced dissociation pathway of the dimer structure of the central structure of the most populated cluster during the first 200 ns of the simulation of structure of the dimer during SMD simulation (5 nm/ns pulling rate). (**a**) The snapshots of dimer structure are from **1**, 0 ns; **2**, 0.2 ns; **3**, 0.6 ns; **4**, 1.4 ns of the SMD trajectory. Cyan indicates random meander; green represents β-turn and H-bonds are yellow dotted lines. N and C indicate the N- and C-terminal ends, respectively. (**b**) Force curves acquired from SMD simulation.

Molecular Dynamics Simulation of the Dimer Structure Using OPLS-AA/L and Amber ff99sb*-ILDN and Force Fields

To test whether applying different force fields would affect the stability of the dimer, the starting structure for the SMD simulation was submitted to 400 ns and 1.1 μs MD simulations using the OPLS-AA/L[2] and the Amber ff99sb*-ILDN[3] force fields, respectively. For the simulation using the Amber ff99sb*-ILDN force field, the dimer structure was solvated in a truncated octahedron with 3092 TIP3P water molecules so that the minimal distance of the peptide from edge of the octahedron was 1 nm. The long-range electrostatic interaction was calculated using the PME method with 0.9 nm cutoff distance and 0.15 nm Fourier spacing. The rest of the simulation parameters were the same as for the dimer simulation. For the simulation using the OPLS-AA/L force field, the parameters were as for the dimer simulation. Trajectories were analyzed using the DSSP method[4] and the GROMOS method of clustering[5]. For clustering, without N- and C-terminal residues, the backbone RMSD cutoff of 0.3 nm was used. For the simulation using the Amber ff99sb*-ILDN force field, the distance between the center of mass of Cys^{13} of chain A (COM13A) and center of mass of Cys^{13} of chain B (COM13B) was calculated. Simulations and trajectory analysis were performed using the GROMACS 4.5.4 package[6].

During the simulation using the OPLS-AA/L force field the antiparallel β-sheet structure of the dimer remained prevalent for the entire 400 ns (Figure S11). The largest cluster of the trajectory contained 82.15% of the explored structures. The representative structure of the largest cluster is shown in Figure S11b.

DSSP analysis of the trajectory of the simulation (Figure S12) using the Amber ff99sb*-ILDN force field revealed that at 420 ns the antiparallel β-sheet structure of the dimer was converted to a more flexible turn/bend conformations. After about 200 ns, however, a more extended antiparallel β-sheet structure was formed and remained stable until end of the simulation. The largest cluster of the trajectory had 42.9% of the explored structures. The representative structure of the largest cluster is shown in Figure S12b.

Changes in structure of the dimer also was followed be calculating the distance between COM13A and COM13B. During the initial 300 ns period, the distance fluctuated at 2 nm and the dimer retained its initial antiparallel β-sheet structure (structure **1** on Figure S13a). Between 400 ns and 600 ns the distance between COM13A and COM13B decreased to ~ 1 nm (structures **2** and **3** on Figure S13) and the β-strands unfolded to random meander conformations. After 600 ns, however, the distance between COM13A and COM13B increased to ~ 2.5 nm and the antiparallel β-sheet conformation was formed again (structures **4**, **5** and **6** on Figure S13a). The β sheet structure of the dimer during the first 300 ns on average stabilized by five backbone hydrogen bonds (Figure S13b), as the antiparallel β-sheet structure unfolded the number of hydrogen bonds decreased and upon refolding to antiparallel β-sheet structure, after 600 ns, the dimer was stabilized on average by seven hydrogen bonds.

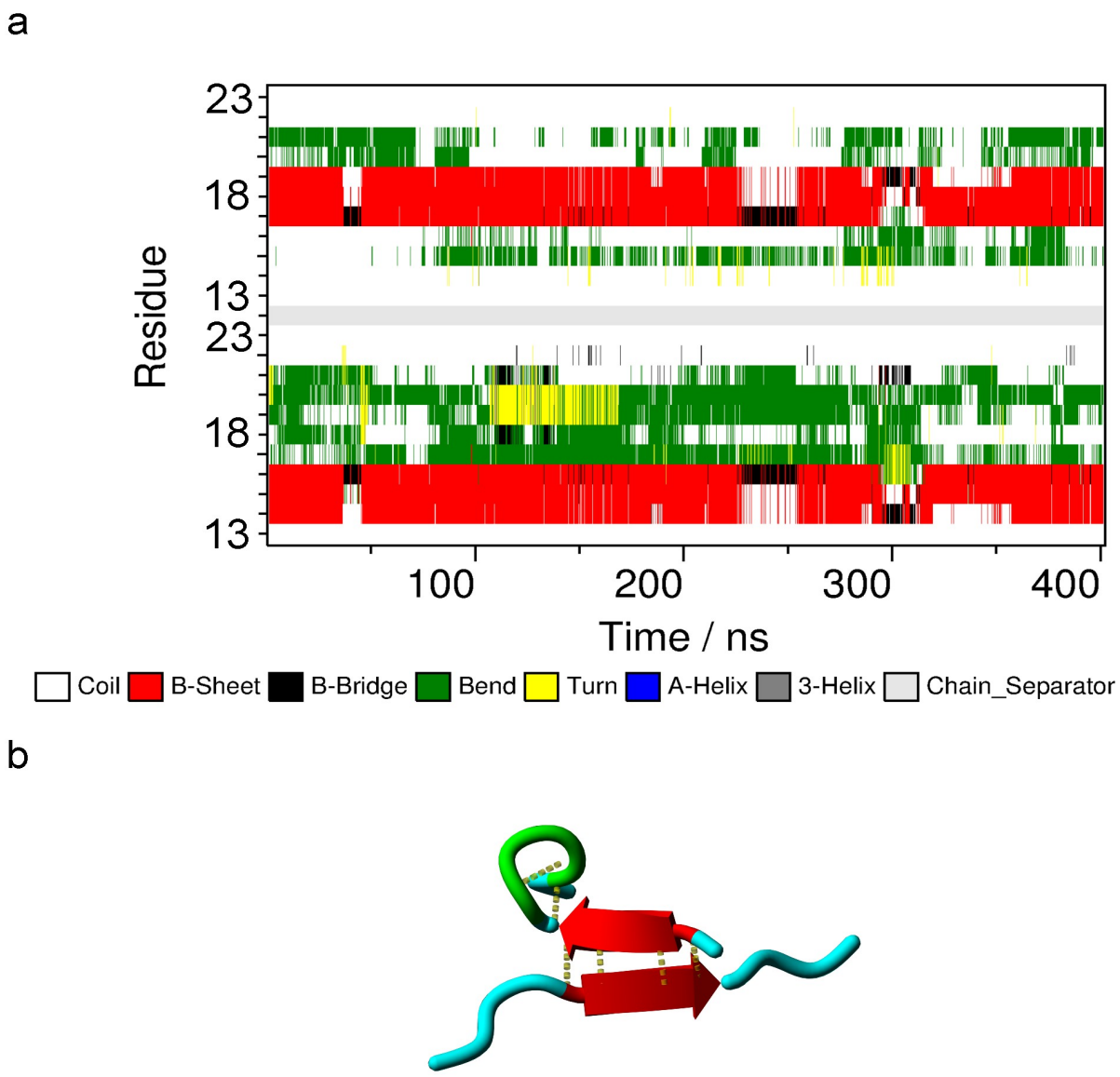

Figure S11. MD simulation using the OPLS-AA/L force field. (**a**) DSSP analysis of the trajectory. Bottom panel, chain A; top panel, chain B. White is coil, black is bridge, green is bend, yellow is β-turn, blue is α-helix, gray is 3_{10} helix and red is β-sheet. The two chains are separated by a light gray ribbon. (**b**) Representative structure of the largest cluster. The snapshot is taken from the trajectory at 114.2 ns. Backbone conformation of the peptide chains is as follows: cyan is random meander; green is β-turn/bend, red arrow is β-sheet and H-bonds are yellow dotted lines.

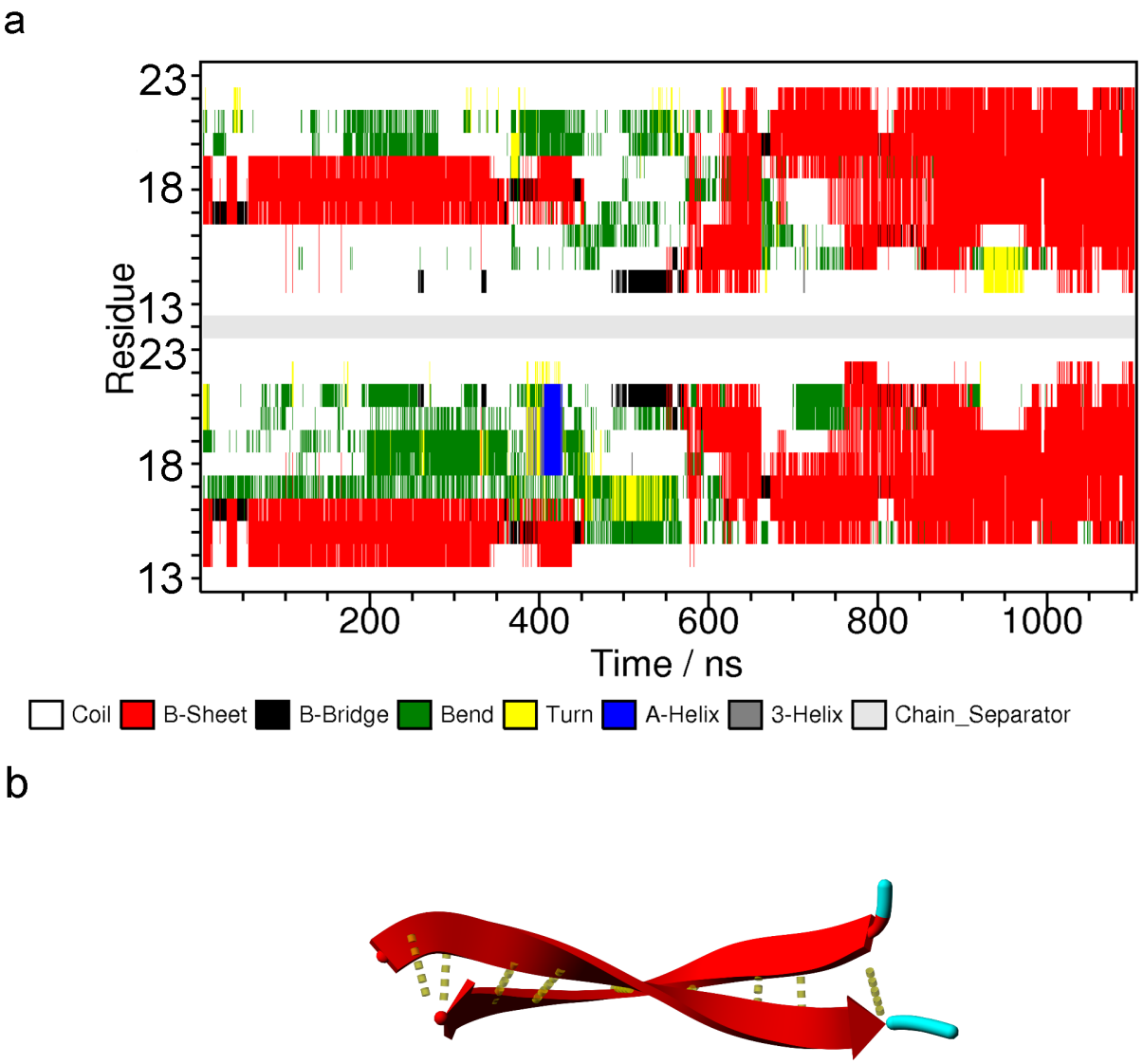

Figure S12. MD simulation using Amber-ff99sb*-ILDN force field (**a**) DSSP analysis of the trajectory. Bottom panel, chain A; top panel, chain B. White is coil, black is bridge, green is bend, yellow is β-turn, blue is α-helix, gray is 3_{10} helix and red is β-sheet. The two chains are separated by a light gray ribbon. (**b**) Representative structure of the largest cluster. The snapshot is taken from the trajectory at 1003.7 ns. Backbone conformation of the peptide chains is as follows: cyan is random meander, red arrow is β-sheet and H-bonds are yellow dotted lines.

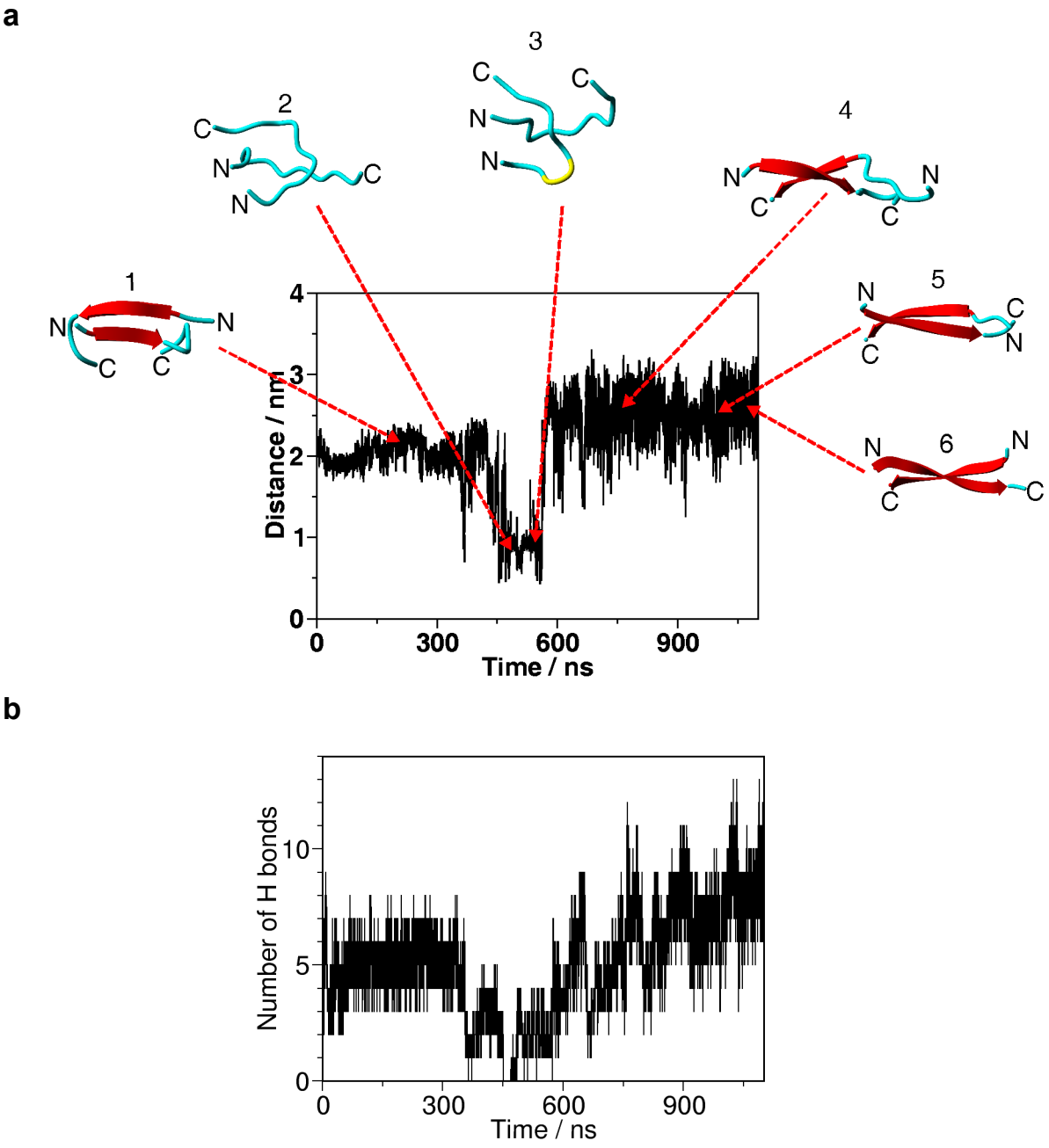

Figure S13. (**a**) The distance between the center of mass of Cys^{13} of chain A and the center of mass of Cys^{13} of chain B in during the 1.1 μs MD simulation of the dimer structure using Amber-ff99sb*-ILDN force field. Snapshots from the trajectory are placed inside the plot. **1**, 200 ns; **2**, 480 ns; **3**, 510 ns; b, 750 ns; **5**, 1000 ns; **6**, 1003.7 ns. Cyan is random meander;yellow is turn; red arrow is β-sheet. N and C indicate the N-and C-termini, respectively. (**b**) Number of hydrogen bonds during MD simulation of the dimer structure using Amber-ff99sb*-ILDN force field.

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