Supporting Information

Structural perturbation of monomers determines the amyloid aggregation propensity of calcitonin variants

Yuying Liu[1,2], Ying Wang[1],Yu Zhang[1], Yu Zou[3], Guanghong Wei[2], Feng Ding[4]*, Yunxiang Sun[1,2,4]*

[1]Department of Physics, Ningbo University, Ningbo 315211, China

[2]State Key Laboratory of Surface Physics and Department of Physics, Fudan University, Shanghai 200433, P. R. China

[3]Department of Sport and Exercise Science, Zhejiang University, Hangzhou 310058, China.

[4]Department of Physics and Astronomy, Clemson University, Clemson, SC 29634, USA.

*E-mail: fding@clemson.edu, sunyunxiang@nbu.edu.cn;

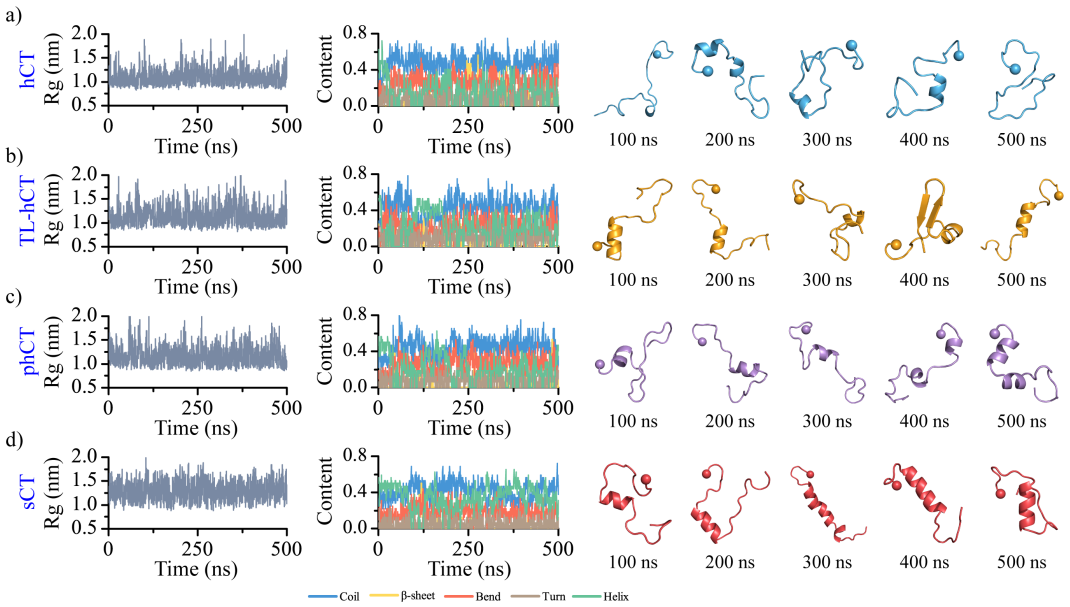

Figure S1. The equilibrium assessments of the hCT, TL-hCT, phCT, and sCT monomeric simulations. The time evolution of radius gyration, each secondary structure's content (β-sheet, helix, coil, bend, and turn), and snapshots for one representative trajectory randomly selected from 30 independent DMD simulations of hCT (a), TL-hCT (b), phCT (c), and sCT (d).

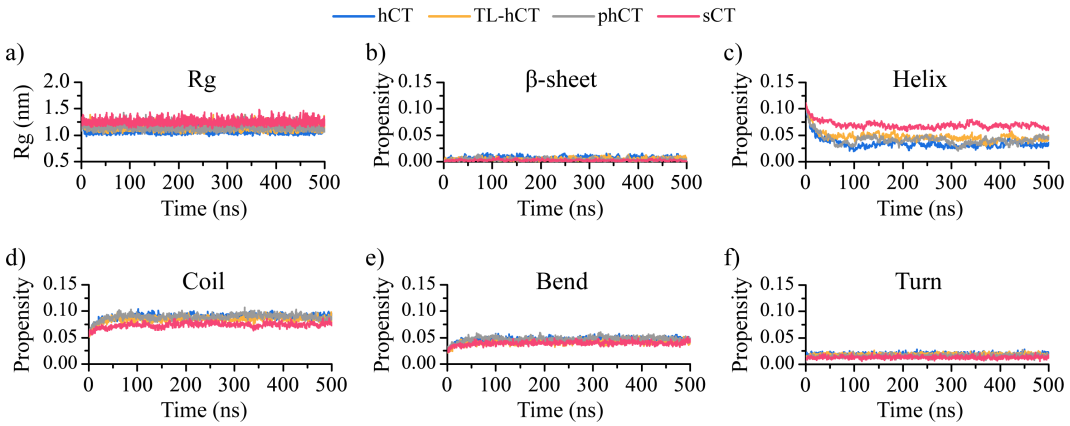

Figure S2. The convergence assessments for the hCT, TL-hCT, phCT, and sCT monomeric simulations. (a) The time evolution of radius gyration and (b-f) each secondary structure's content (β-sheet, helix, coil, bend, and turn) averaged over all 30 independent DMD simulations of hCT(blue), TL-hCT(yellow), phCT(grey), and sCT(red).

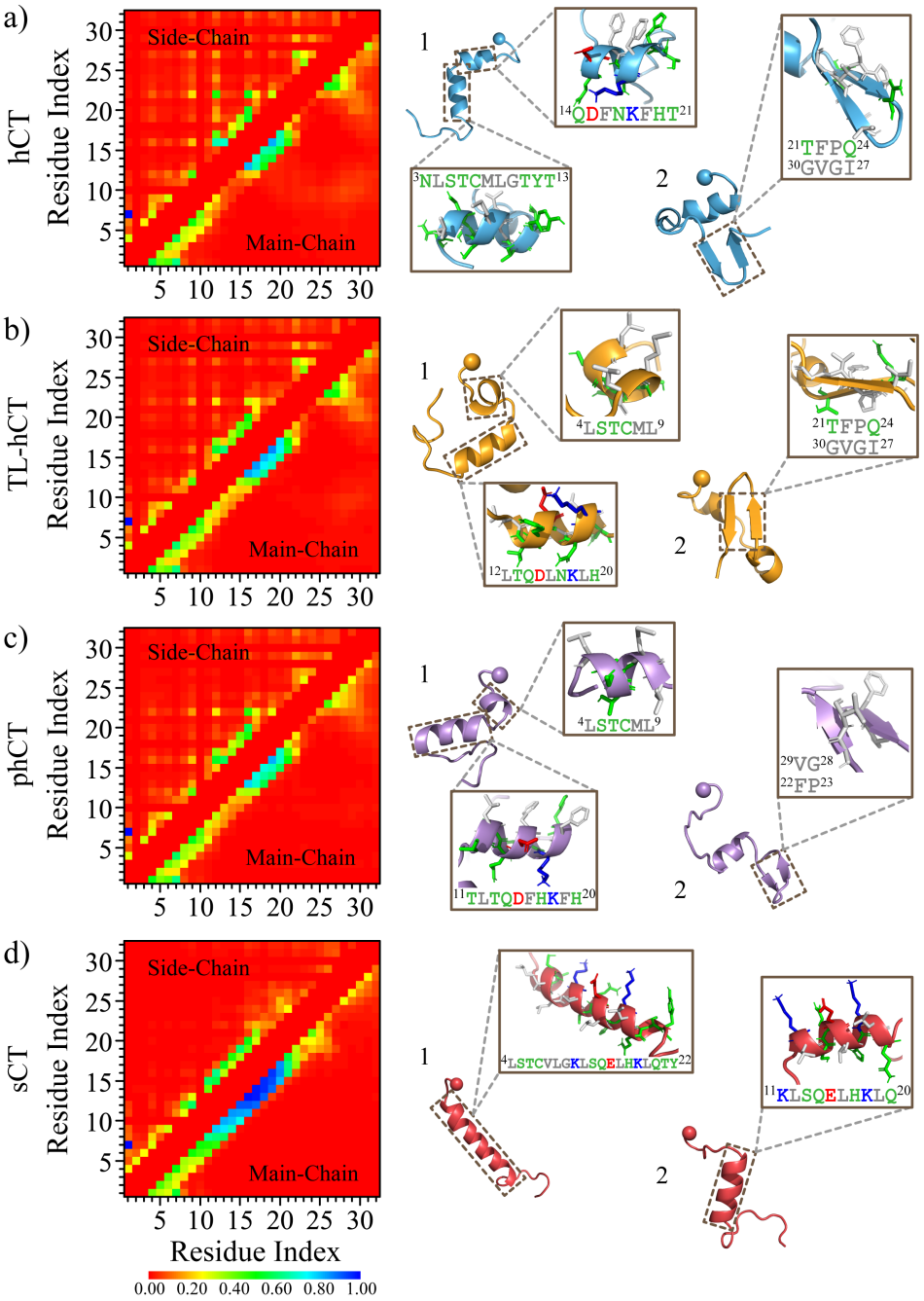

Figure S3. Residue-pairwise contact frequency analysis for each calcitonin monomer. The residue-pairwise contact frequencies formed by atoms from main-chain (lower diagonal) and side-chain (upper diagonal) atoms during the last 200 ns of 30 independent 500 ns DMD simulations of (a) hCT, (b) TL-hCT, (c) phCT, and (d) sCT monomers. Representative contact patterns heightened by boxes and the corresponding structures are also presented.

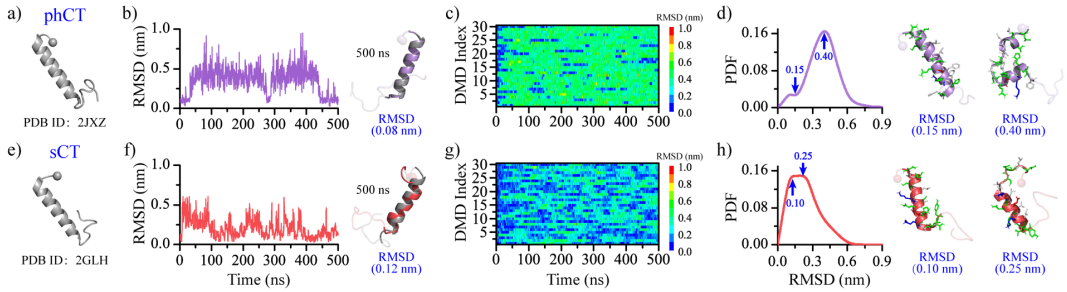

Figure S4. Root-mean-square deviation (RMSD) of phCT and sCT corresponding to the NMR determined structures. The NMR experiments determined structures of phCT (a) and sCT (e). The time evolution of the backbone RMSD of phCT (b) and sCT (f) corresponds to the helical region (residues 3-22) in the NMR characterized structure for one representative trajectory. The final snapshots are also presented and compared with the NMR characterized structures (colored grey). The time evolution of backbone RMSD corresponding to the helical regions in the NMR characterized structure of phCT (c) and sCT (g) for all 30 independent trajectories. The conformational probability distribution as a function of the helical region RMSD for phCT (d) and sCT (h) during the last 200 ns from 30 independent DMD trajectories.

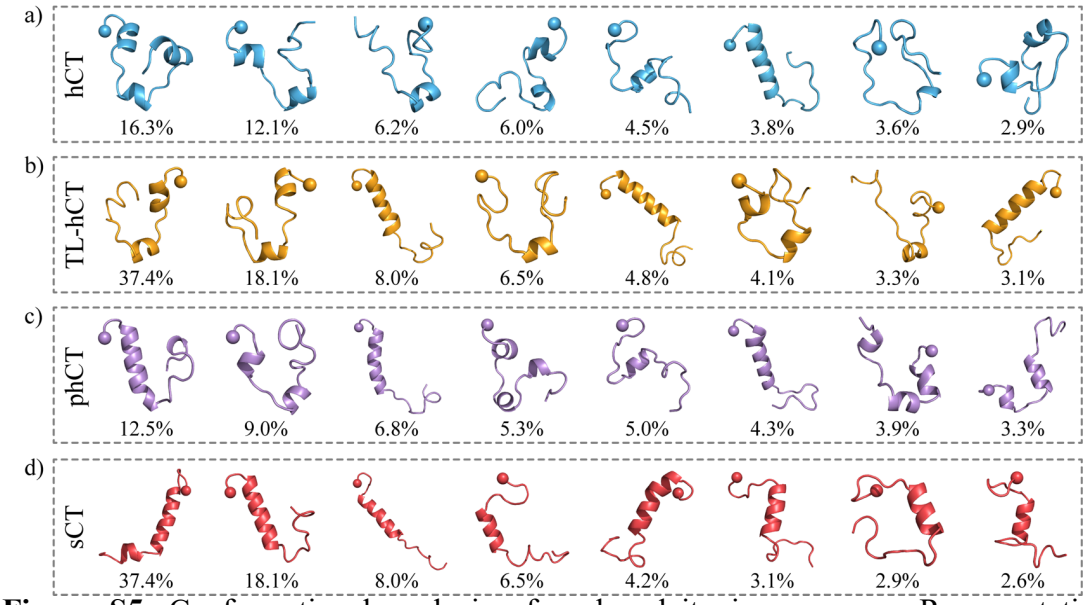

Figure S5. Conformational analysis of each calcitonin monomer. Representative conformations of the top 8 most-populated clusters of hCT (a), TL-hCT (b), phCT (c), and sCT (d). All calcitonin monomers from the last 200 ns of 30 independent DMD trajectories in each molecular system were used for the cluster analysis.

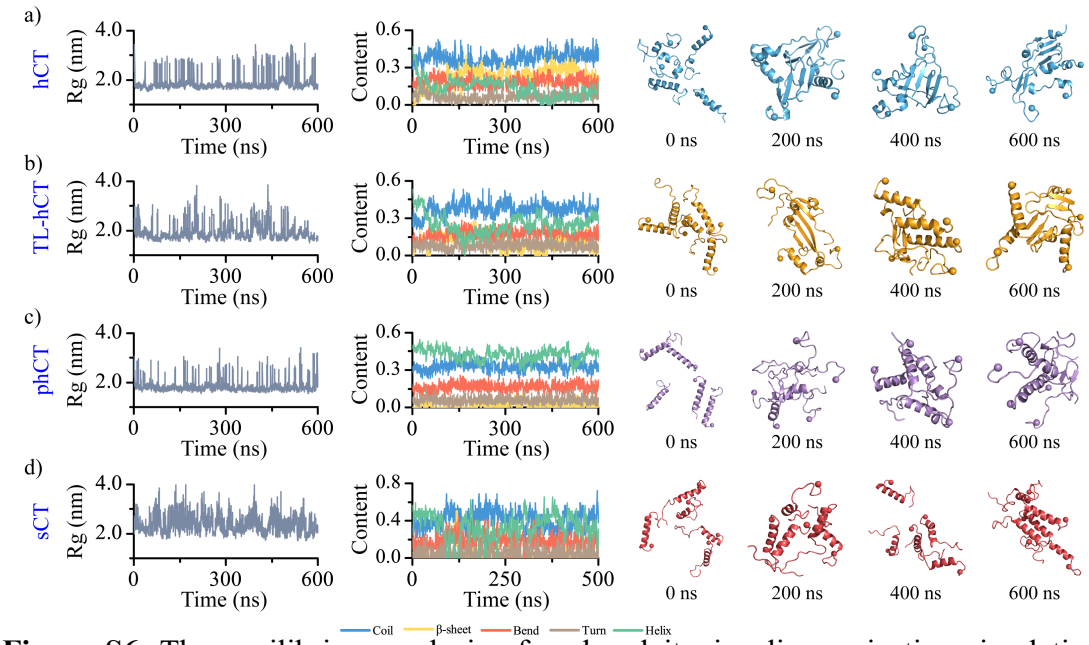

Figure S6. The equilibrium analysis of each calcitonin oligomerization simulation. The time evolution of radius gyration, each secondary structure's content (β-sheet, helix, coil, bend, and turn), and snapshots of hCT (a), TL-hCT (b), phCT (c), and sCT (d). For each molecular system, only one trajectory randomly selected from 30 independent DMD simulations is presented.

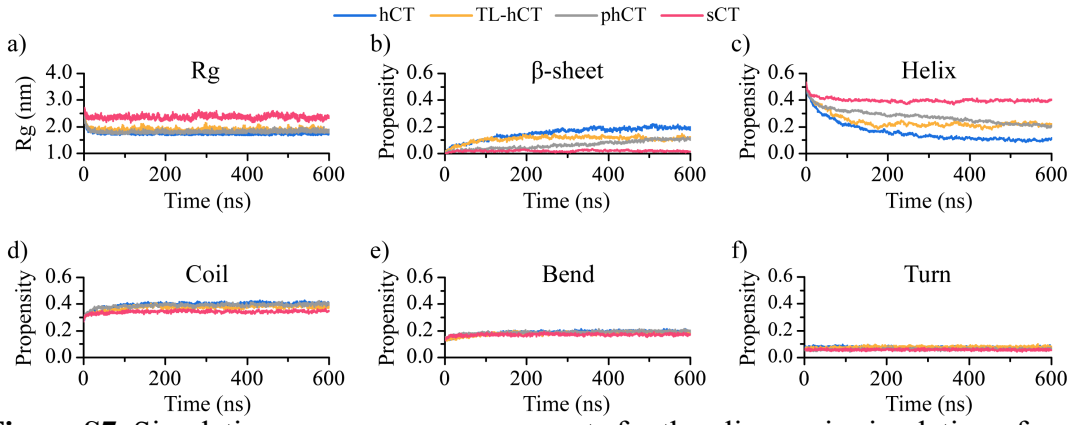

Figure S7. Simulation convergence assessments for the oligomeric simulation of each type of calcitonin peptide. (a) The time evolution of radius gyration and (b-f) each secondary structure's (β-sheet, helix, coil, bend, and turn) content averaged over all 30 independent 600ns DMD simulations of hCT(blue), TL-hCT(yellow), phCT(grey), and sCT(red).

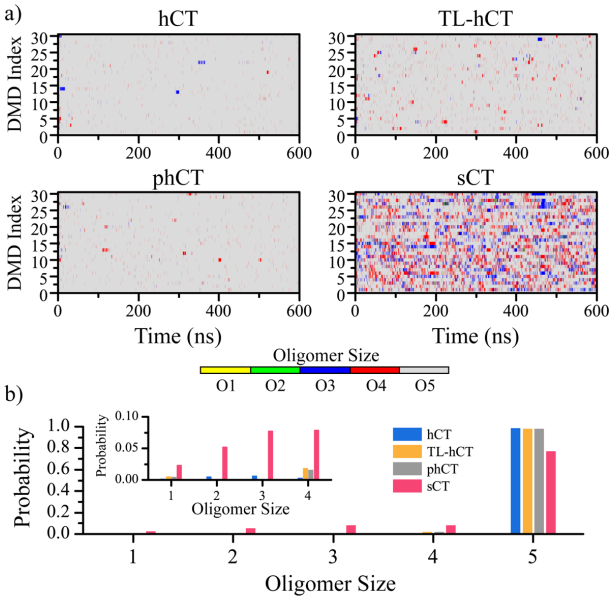

Figure S8. (**a**) The time evolution of the largest oligomer size into which a peptide aggregated in each DMD simulation trajectory is shown to illustrate the conformational dynamics of hCT, TL-hCT, phCT, and sCT system. (b) The size distributions of oligomers formed by each calcitonin peptide during the last 300 ns of 30 independent 600 ns DMD simulations.

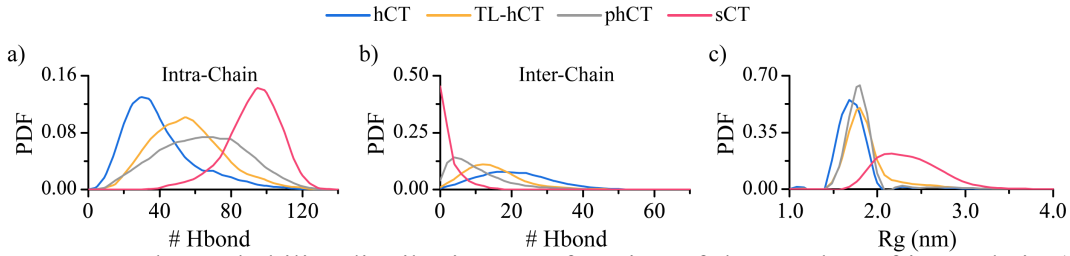

Figure S9. The probability distribution as a function of the number of intra-chain (a) and inter-chain (b) hydrogen bonds formed by main-chain atoms, and (c) radius of gyration. Only structures in the last 300 ns of all independent DMD simulations were used for the analysis.