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

Mechanistic insights into the inhibition of amyloid-β aggregation by chitosan

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Supplementary Information

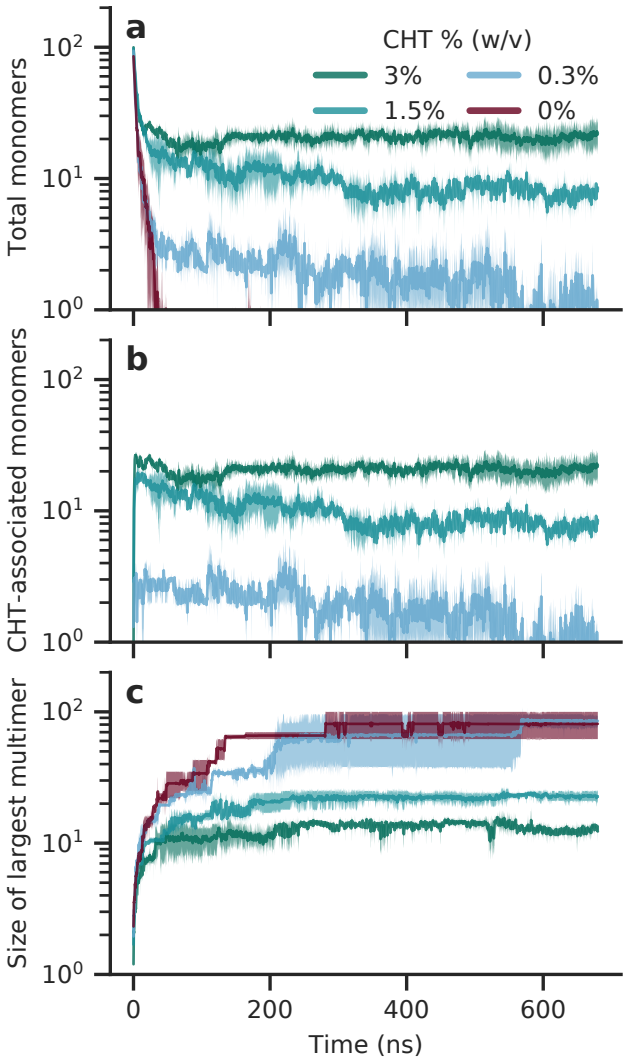

Figure S1: Time evolution of Aβ aggregation at pH 6.5, with 0, 0.3, 1.5, and 3.0 % CHT measured by total population of monomers (a), CHT-associated subpopulation of monomers (b), and size of the largest multimers (c). Time series are averaged over two independent runs, and the shaded regions denote standard deviation.

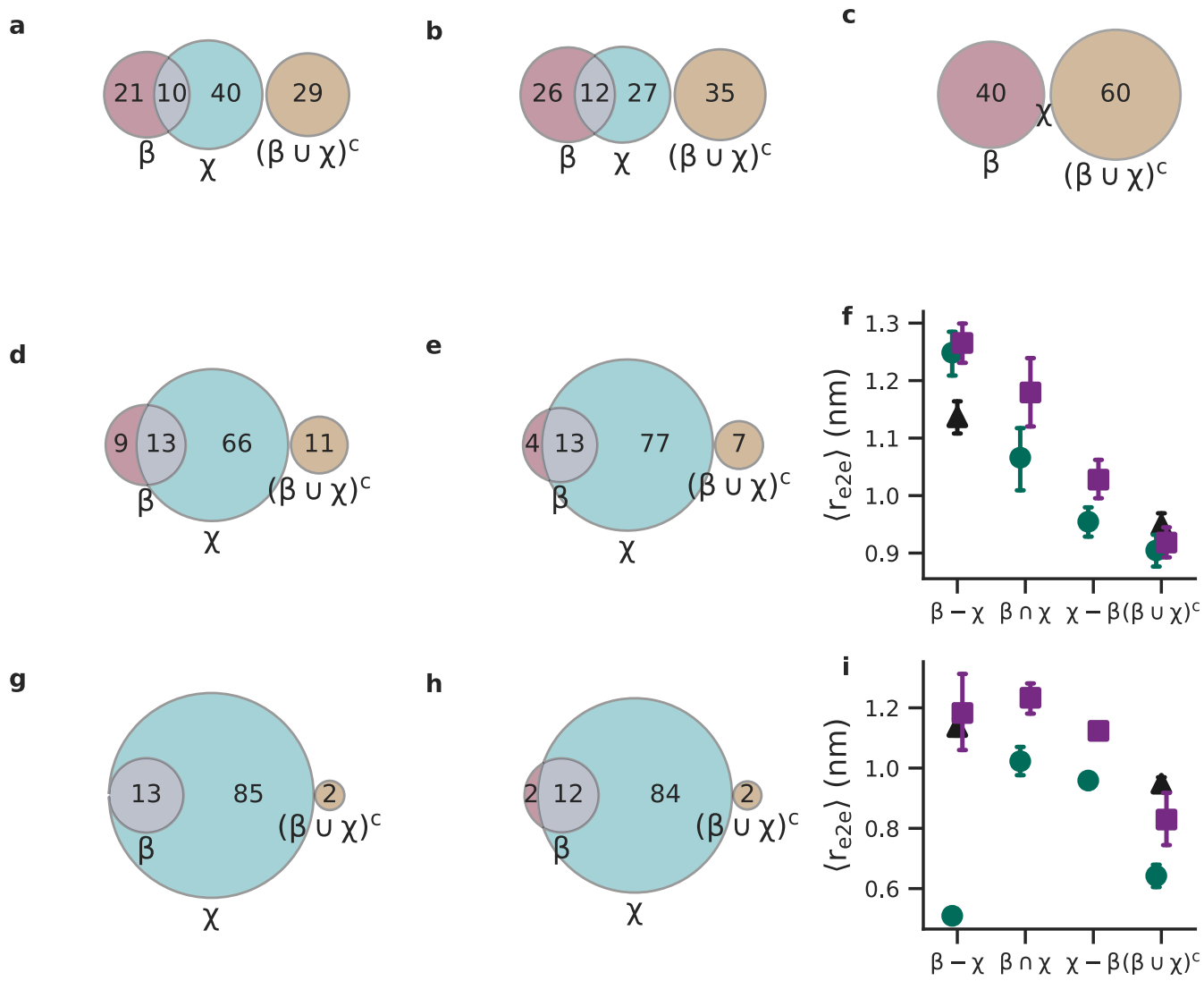

Figure S2: (a, b, c, d, e, g, h) Population percentages of peptides belonging to various subsets, classified based on the presence of beta-sheet secondary structure (set β), and direct contact with CHT (set χ). Data for 0% (w/v) CHT are shown in (c). Data for pH 7.5, at 0.3, 1.5, and 3.0% CHT are shown in (a), (d), and (g), respectively. Data for pH 6.5, at 0.3, 1.5, and 3.0% CHT are shown in (b), (e), and (h), respectively. Comparison of mean end-to-end distances for peptides belonging to the four subsets, for 0.3% CHT and 3.0% CHT, is shown in (f), and (i), respectively (pH 7.5 in green circles ◯, pH 6.5 in purple squares □, and 0% CHT in black triangles △).

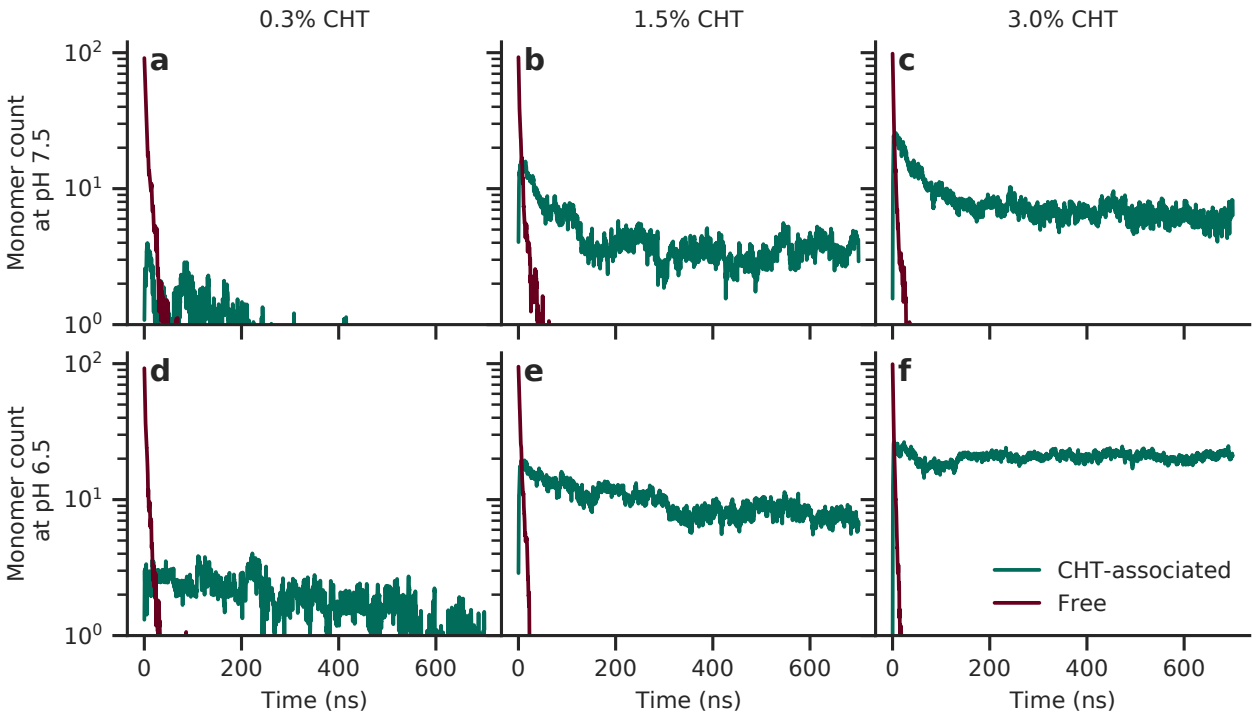

Figure S3: Comparison of populations of free monomers, and CHT-associated monomers over time for 0.3, 1.5, and 3.0% CHT at pH 7.5 (a, b, c) and pH 6.5 (d, e, f). Maroon traces represent free monomer populations and green traces represent CHT-associated monomer populations.

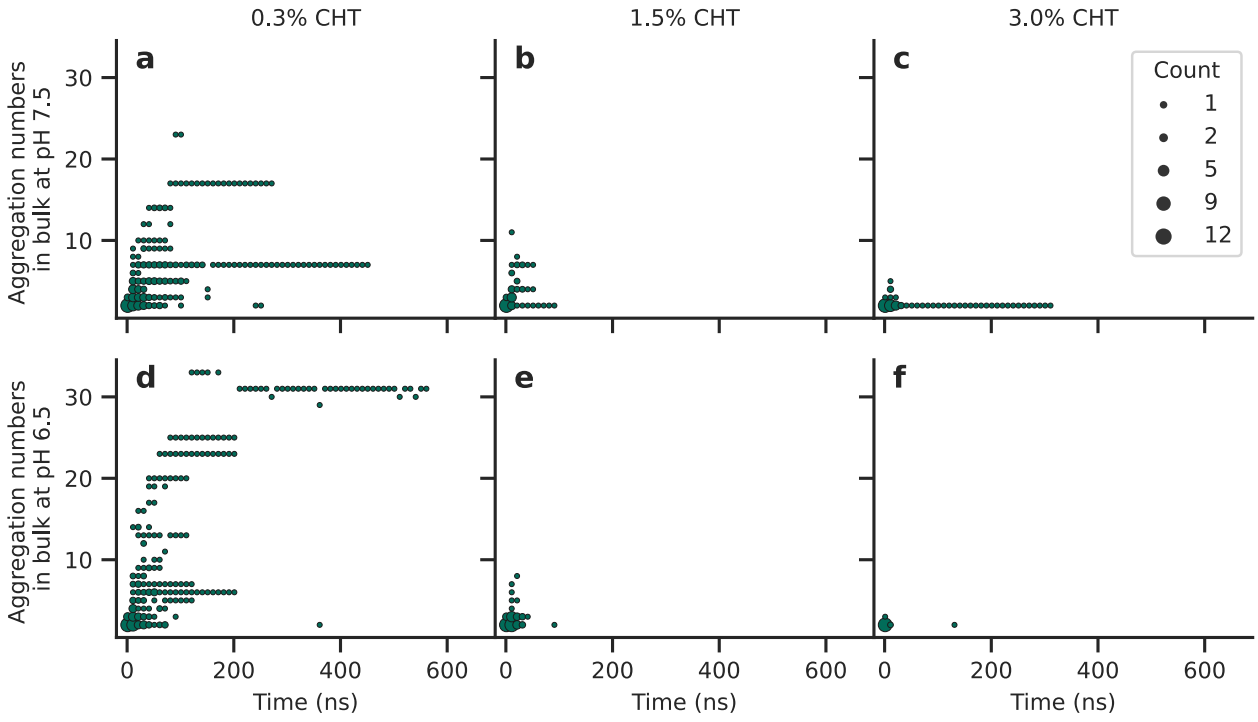

Figure S4: Aggregation numbers of multimers present in the bulk as a function of time for 0.3, 1.5, and 3.0% CHT at pH 7.5 (a, b, c) and pH 6.5 (d, e, f). A multimer was considered to be in the bulk if none of the constituent peptides were in contact with CHT. The diameters of the markers indicate the number of times that an aggregation number was observed at a time (see legend in (c)). Data were aggregated over two independent runs, and plotted every 10 ns.

Residue	Bead name	Bead type
K, lysine	BB*	PP5*
	S1	C3
	S2	Qd
L, leucine	BB*	PP5*
	S1	C1
V, valine	BB*	PP5*
	S1	C1
F, phenylalanine	BB*	PP5*
	S1	C3
	S2	C3
A, alanine	BB*	PP5*
E, glutamate	BB*	PP5*
	S1	C3
	S2	Qa
N-glucosamine, unprotonated	B1	P1
	B2	P2
	B3	P5
N-glucosamine, protonated	B1	P1
	B2	P2
	B3	Qd
PW, MARTINI polarizable solvent	W*	POL*

Table S1: Coarse-grained bead names, and bead types for amino acid residues in the Aβ fragment $K_{16}LVFFAE_{22}$, protonated and unprotonated N-glucosamine saccharide units of CHT, and the MARTINI polarizable solvent mdoel. Polarized beads are indicated with an asterisk (*); these beads contain internal dummies of equal and opposite charges. W beads have dummies of type D and charge ± 0.46.[1] BB beads have dummies of type D2 and charge ± 0.34.[2]

Bead type	PP5	P5	P2	P1	Qd	Qa	C3	C1	POL
PP5	5.00^a	5.60	5.60	5.60	5.32^a	5.32^a	2.70	2.00	4.75^a
P5	5.60	5.60	5.60	5.60	5.60	5.60	2.70	2.00	5.32
P2	5.60	5.60	4.50	4.50	5.60	5.60	3.10	2.30	4.30
P1	5.60	5.60	4.50	4.50	5.60	5.60	3.50	2.70	4.30
Qd	5.32^a	5.60	5.60	5.60	3.50	4.00	2.70	2.30	5.00
Qa	5.32^a	5.60	5.60	5.60	4.00	3.50	2.70	2.30	5.00
C3	2.70	2.70	3.10	3.50	2.70	2.70	3.50	3.50	2.70
C1	2.00	2.00	2.30	2.70	2.30	2.30	3.50	3.50	1.00^a
POL	4.75^a	5.32	4.30	4.30	5.00	5.00	2.70	1.00^a	4.00

Table S2: Non-bonded Lennard-Jones well depths (ϵ, in units of kJ/mol) for the main-bead (i.e., not dummy charge) types used to model CHT, Aβ, and solvent molecules. The van der Waals interaction diameter, (σ), for main-bead interactions is 0.47 nm. Values marked with the superscript, a, were reparameterized by Sahoo *et. al.* for WEPPROM.[3] Unmarked interactions are borrowed directly from MARTINI.[4] Dummy charges with bead type D, which interact at $\epsilon = 0\ kJ/mol$ and $\sigma = 0\ nm^1$ with each other, and all other bead types except D2. Interactions with dummy charges with bead type D2 have a small repulsive core expressed by the Lennard-Jones repulsive term $C12 = 4.5355 \times 10^{-10}\ kJ\ nm^{12}/mol$, and an attractive term $C6 = 0\ kJ\ nm^6/mol$.[2,5]

References

[1] S. O. Yesylevskyy, L. V. Schäfer, D. Sengupta and S. J. Marrink, *PLOS Computational Biology*, 2010, **6**, e1000810.

[2] S. J. Ganesan and S. Matysiak, *Journal of Chemical Theory and Computation*, 2014, **10**, 2569–2576.

[3] A. Sahoo, H. Xu and S. Matysiak, *Physical Chemistry Chemical Physics*, 2019, **21**, 8559–8568.

[4] D. H. de Jong, G. Singh, W. F. D. Bennett, C. Arnarez, T. A. Wassenaar, L. V. Schäfer, X. Periole, D. P. Tieleman and S. J. Marrink, *Journal of Chemical Theory and Computation*, 2013, **9**, 687–697.

[5] S. J. Ganesan, H. Xu and S. Matysiak, *Physical Chemistry Chemical Physics*, 2016, **18**, 17836–17850.