

Electronic Supplementary Information
to
**Glycation Induces Conformational Changes in Amyloid- β Peptide and Enhances its
Aggregation Propensity: Molecular Insights**

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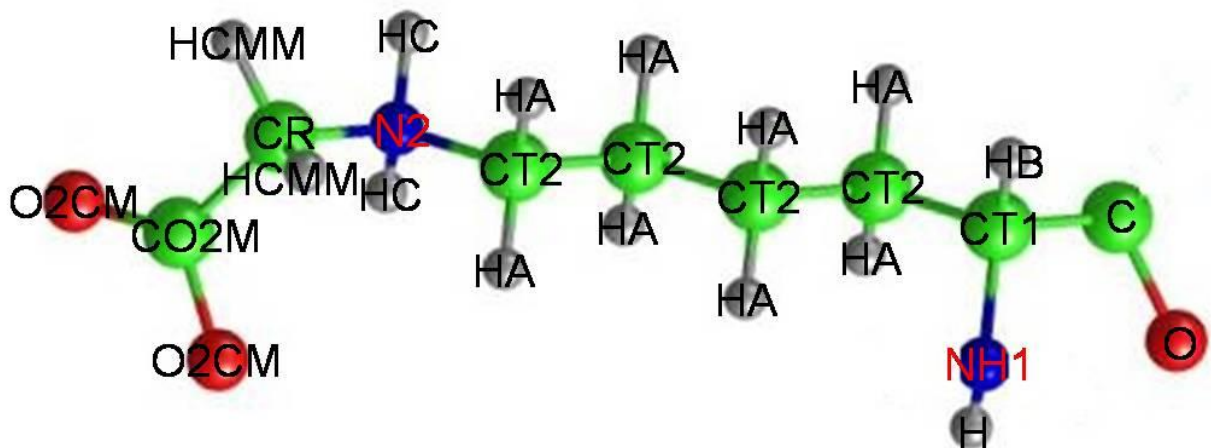


Figure S1. Glycated lysine residue with atom names used in the modified force field. Corresponding force field parameters are provided in Tables S1a to S1f

Non-bonded Lennard-Jones Potential,

$$V_{i,j} = E_{ps,i,j} \left[\left(\frac{R_{min,i,j}}{r_{i,j}} \right)^{12} - 2 \left(\frac{R_{min,i,j}}{r_{i,j}} \right)^6 \right]$$

TableS1a.

Atom <i>i</i>	E_{ps} (kcal mol ⁻¹)	$R_{min}/2$ (Å)
NRP	-0.200000	1.850000
HNRP	-0.046000	0.224500
CR	-0.055000	2.175000
HCMM	-0.022000	1.320000
CO2M	-0.070000	2.000000
O2CM	-0.120000	1.700000

Cross interactions between dissimilar atoms are calculated with Loretz-Berthelot mixing rules incorporated in the NAMD package.

Bonded Potential,

$$V_{i,j} = \frac{1}{2} k_{i,j} (l - l_0)^2$$

Table S1b.

<i>Atom i</i>	<i>Atom j</i>	<i>equilibrium distance l₀ (Å)</i>	<i>k_{ij} (kcal mol⁻¹ Å⁻²)</i>
CO2M	O2CM	1.2610	702.103
NRP	HNRP	1.0280	443.528
NRP	CR	1.4800	276.638
CR	CO2M	1.5100	275.631
CR	HCMM	1.0930	342.991
CR	CR	1.5080	306.432
NH3	CR	1.4800	276.638

Angle bending potential,

$$V_{i,j,k} = \frac{1}{2} k_{i,j,k} (\theta - \theta_0)^2$$

Table S1c.

<i>Atom i</i>	<i>Atom j</i>	<i>Atom k</i>	<i>Equilibrium angle θ₀ (degree)</i>	<i>k_{ijk} (kcal mol⁻¹ rad⁻²)</i>
HNRP	NRP	CR	111.2060	41.452
HNRP	NRP	HNRP	107.7870	41.596
NRP	CR	HCMM	106.2240	62.754
NRP	CR	CR	106.4930	84.848
NRP	CR	CO2M	112.2380	75.420
HCMM	CR	CR	110.5490	45.770
HCMM	CR	CO2M	108.9040	37.782
CR	CR	CO2M	98.4220	23.749
CR	CR	CR	109.6080	61.243
HCMM	CR	HCMM	108.8360	37.134
CR	NRP	CR	112.2510	62.034
CR	CO2M	O2CM	114.6890	87.007
O2CM	CO2M	O2CM	130.6000	84.991
CR	NH3	CT2	112.2510	62.034
NH3	CR	CO2M	112.2380	75.420
NH3	CR	HCMM	106.2240	62.754
HC	NH3	CR	111.2060	41.452

Dihedral potential,

$$V_{\phi} = k_{\phi}^n [1 + \cos(n\phi - \delta)]$$

Table S1d.

Atom <i>i</i>	Atom <i>j</i>	Atom <i>k</i>	Atom <i>l</i>	 (kcal mol ⁻¹)	<i>n</i>	δ (degrees)
NRP	CR	CR	HCMM	0.346	1	0.00
NRP	CR	CR	HCMM	-0.265	2	180.00
NRP	CR	CR	HCMM	0.139	3	0.00
NRP	CR	CR	CR	-0.324	1	0.00
NRP	CR	CR	CR	0.275	2	180.00
NRP	CR	CR	CR	0.295	3	0.00
NRP	CR	CO2M	O2CM	0.300	2	180.00
HNRP	NRP	CR	HCMM	0.130	3	0.00
HNRP	NRP	CR	CR	0.093	3	0.00
HNRP	NRP	CR	CO2M	0.125	3	0.00
CR	CR	CR	HCMM	0.320	1	0.00
CR	CR	CR	HCMM	-0.315	2	180.00
CR	CR	CR	HCMM	0.132	3	0.00
CR	CR	CR	CR	0.051	1	0.00
CR	CR	CR	CR	0.341	2	180.00
CR	CR	CR	CR	0.166	3	0.00
HCMM	CR	CR	HCMM	0.142	1	0.00
HCMM	CR	CR	HCMM	-0.693	2	180.00
HCMM	CR	CR	HCMM	0.157	3	0.00
HCMM	CR	CO2M	O2CM	-0.053	3	0.00
CR	CR	CO2M	O2CM	0.631	2	180.00
HCMM	CR	CR	CO2M	-0.070	3	0.00
CR	CR	CR	CO2M	0.150	3	0.00
CR	CR	NRP	CR	0.125	3	0.00
CR	NRP	CR	HCMM	0.123	3	0.00
CR	NRP	CR	CO2M	0.125	3	0.00
CT2	NH3	CR	HCMM	0.123	3	0.00
CT2	NH3	CR	CO2M	0.125	3	0.00
NH3	CR	CO2M	O2CM	0.300	2	180.00
HC	NH3	CR	HCMM	0.130	3	0.00
HC	NH3	CR	CO2M	0.125	3	0.00

Improper Dihedral Potential,

$$V_{\omega} = k_{\omega}(\omega - \omega_0)^2$$

Table S1e.

<i>Atom i</i>	<i>Atom j</i>	<i>Atom k</i>	<i>Atom l</i>	<i>k_w (kcal mol⁻¹ rad⁻²)</i>	<i>ω₀ (degrees)</i>
NRP	HNRP	CR	HNRP	0.00	0.00
CR	CR	NRP	CO2M	0.00	0.00
CR	CO2M	NRP	HCMM	0.00	0.00
CR	CR	CR	HCMM	0.00	0.00
CR	HCMM	CR	HCMM	0.00	0.00
CR	NRP	CR	HCMM	0.00	0.00
NRP	CR	CR	HNRP	0.00	0.00
CO2M	O2CM	CR	O2CM	12.810	0.00
CR	HCMM	NRP	HCMM	0.00	0.00

Partial Charges of atoms.

Table S1f.

<i>Atom</i>	<i>Charge (units of e)</i>
NH1	-0.47
H	0.31
CT1	0.07
HB	0.09
CT2	-0.18
HA	0.09
NH3	-0.30
HC	0.33
C	0.51
O	-0.51
CR	0.354
HCMM	0.09
CO2M	0.9060
O2CM	-0.9000

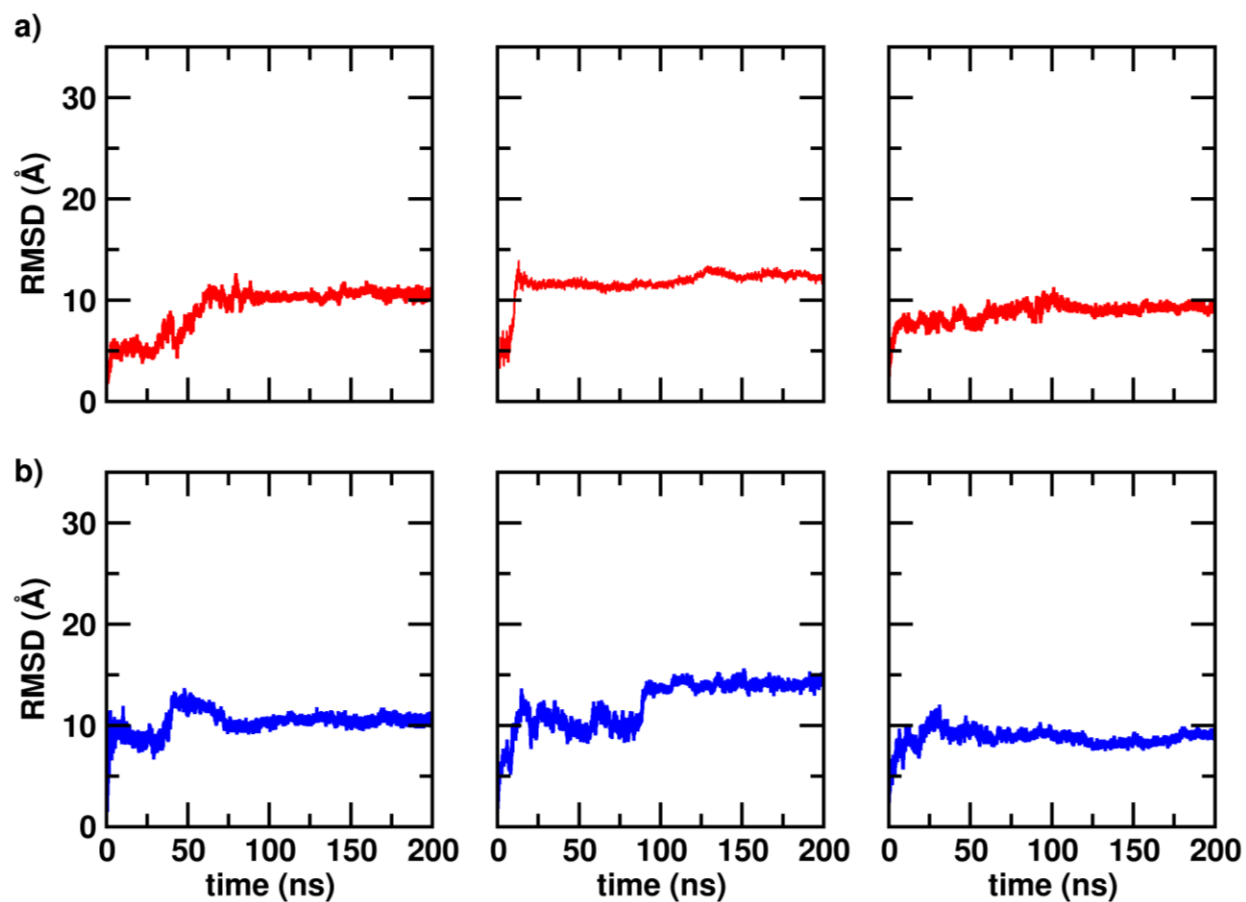


Figure S2. Time evolution of the backbone root mean square deviation (RMSD; in Å) for the three independent trajectories of the a) unglycated and b) glycated oligomeric dimer systems.

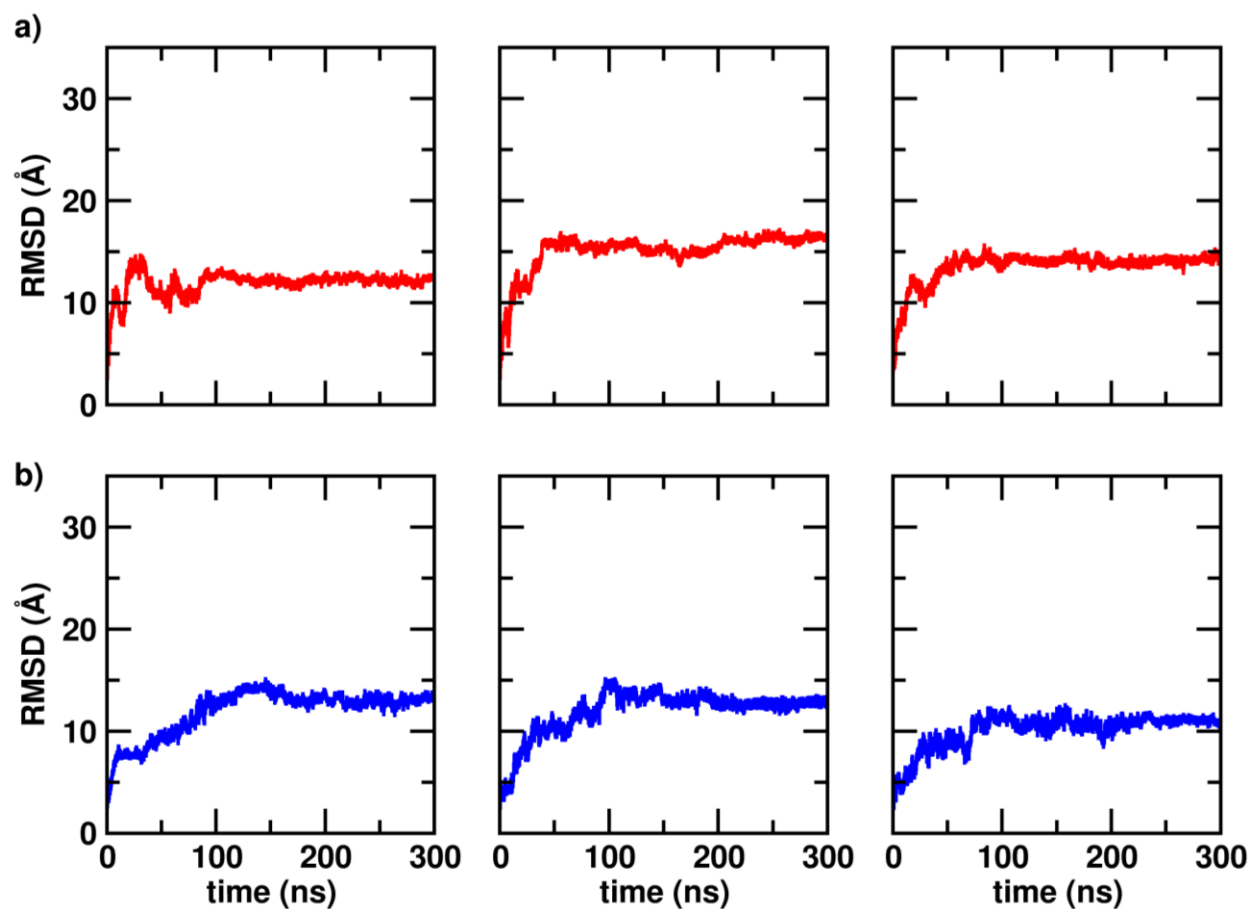


Figure S3. Time evolution of the backbone root mean square deviation (RMSD; in Å) for the three independent trajectories of the a) unglycated and b) glycosylated oligomeric trimer systems.

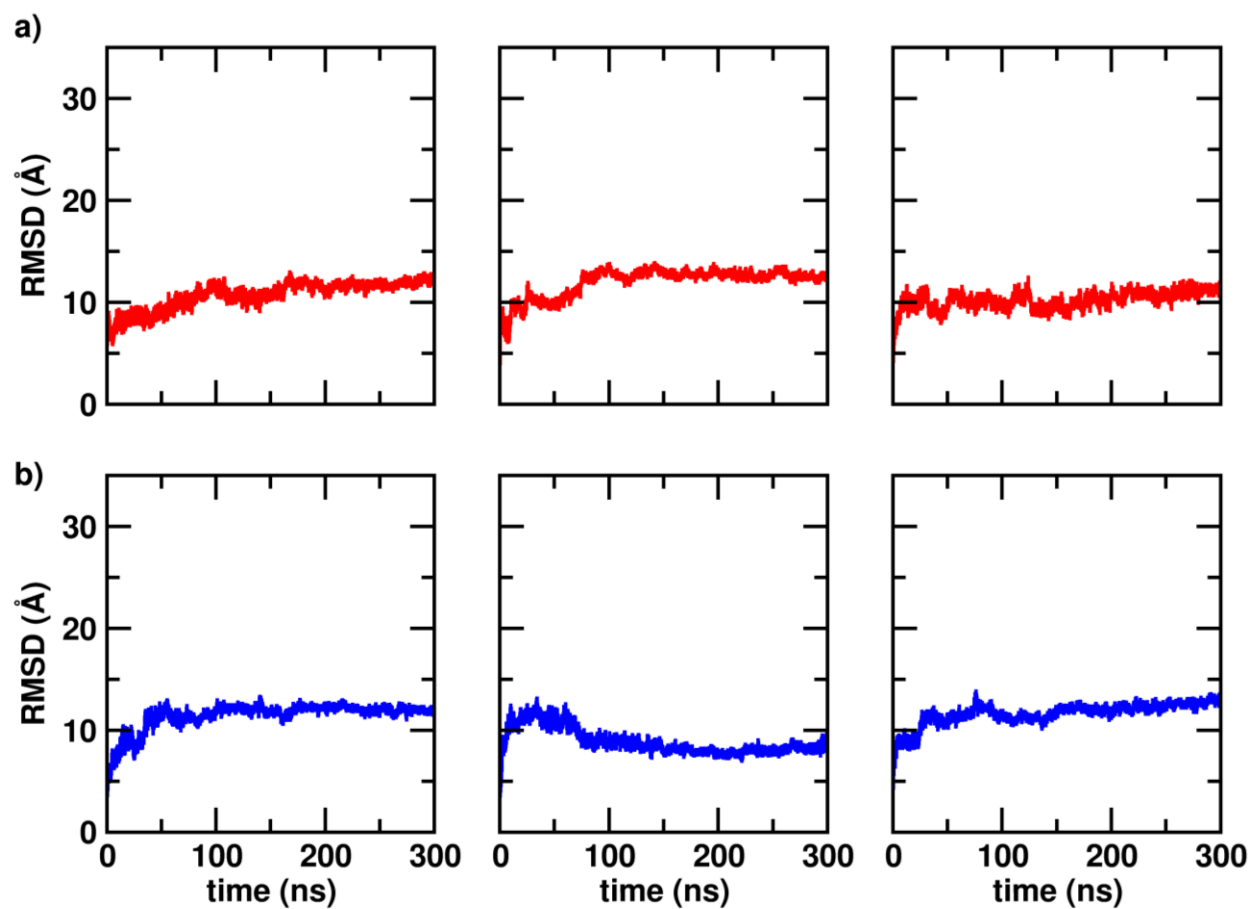


Figure S4. Time evolution of the backbone root mean square deviation (RMSD; in Å) for the three independent trajectories of the a) unglycated and b) glycated protofibrillar systems.

Structural Persistence (P)

The structural persistence, P , of a protein conformation relative to a reference structure is defined as,

$$P = \frac{1}{N_{res}} \sum_{j=1}^{N_{res}} e^{-(\Delta\phi_j / \Delta\phi_{max})} e^{-(\Delta\psi_j / \Delta\psi_{max})}$$

In the formula above, N_{res} is the number of residues; $\Delta\phi_j$ and $\Delta\psi_j$ are the absolute values of the changes in dihedral angles ϕ and ψ of the j^{th} residue relative to values in the reference structure; and $\Delta\phi_{max}$ and $\Delta\psi_{max}$ are the maximum alterations possible in the dihedral angles within the Ramachandran diagram. Thus $P=1$ defines a conformation which is completely unchanged relative to the reference structure, and stability in the value of P during the course of a trajectory indicates the attainment of conformational stability.

In previous work carried out in our group, the P value of a protein has been found to be a good indicator of the structural stability of a protein over simulation trajectories and within cumulative conformational ensembles obtained from independent trajectories; these works have been cited below.¹⁻³

In the present study, we have calculated the P value of each peptide along each independent dimeric and trimeric trajectory in order to evaluate conformational stability. The reference structure in each case is the initial configuration. This data is represented in Figures S5 to S10.

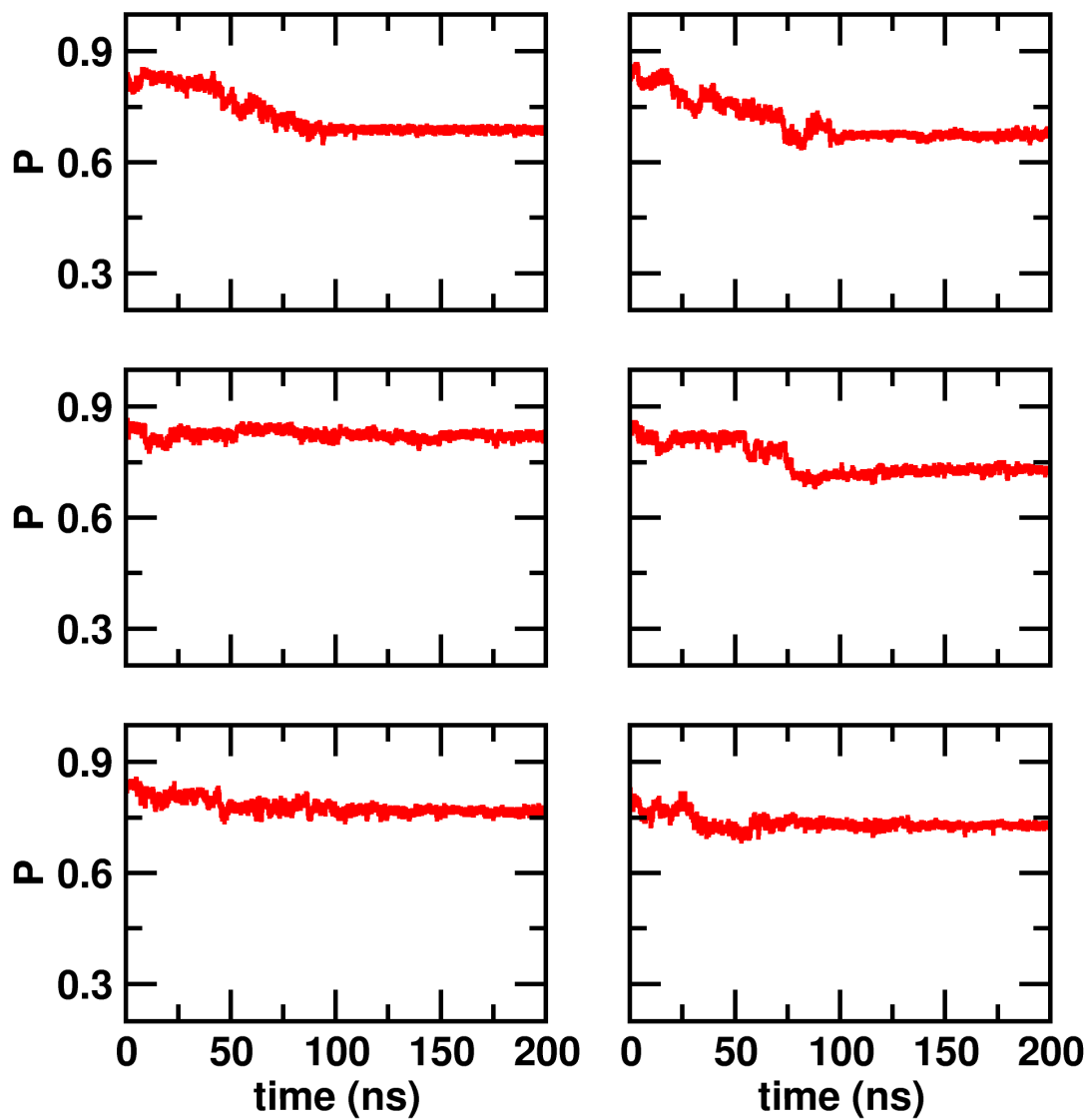


Figure S5. Time evolution of structural persistence, P , for three independent trajectories of unglycated oligomeric dimer systems.

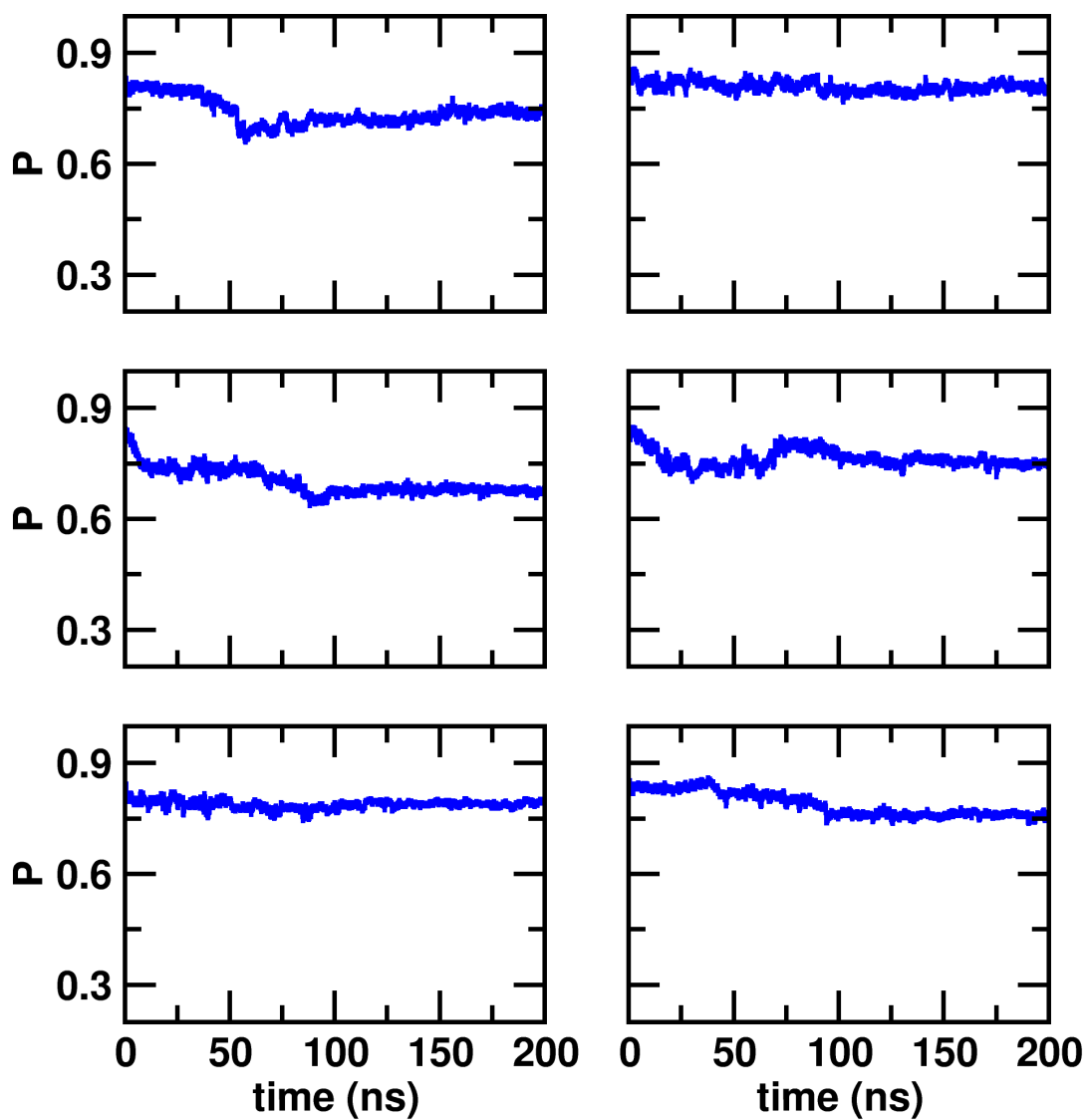


Figure S6. Time evolution of structural persistence, P , for three independent trajectories of glycosylated oligomeric dimer systems.

<i>System</i>	<i>trajectory1</i>		<i>trajectory2</i>		<i>trajectory3</i>	
	<i>pep 1</i>	<i>pep 2</i>	<i>pep 1</i>	<i>pep 2</i>	<i>pep 1</i>	<i>pep 2</i>
Unglycated dimer	0.69 (0.01)	0.67 (0.01)	0.82 (0.01)	0.72 (0.01)	0.77 (0.01)	0.73 (0.01)
Glycated dimer	0.73 (0.02)	0.8 (0.02)	0.68 (0.01)	0.75 (0.01)	0.79 (0.01)	0.76 (0.01)

Table S2. Mean values of structural persistence, P , of unglycated and glycated oligomeric dimer systems averaged over last 100 ns of each trajectory. Standard deviations are provided within braces.

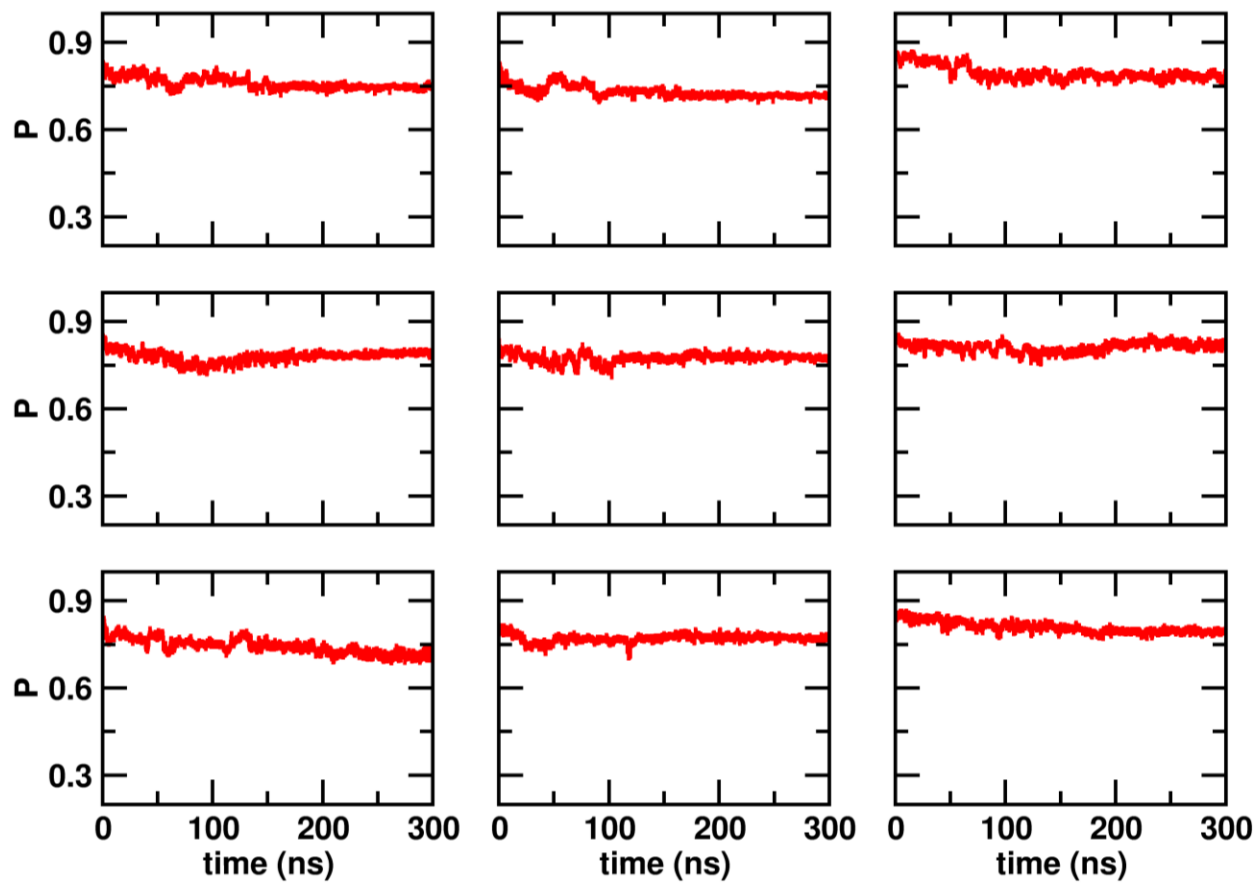


Figure S7. Time evolution of structural persistence, P , for three independent trajectories of unglycated oligomeric trimer systems.

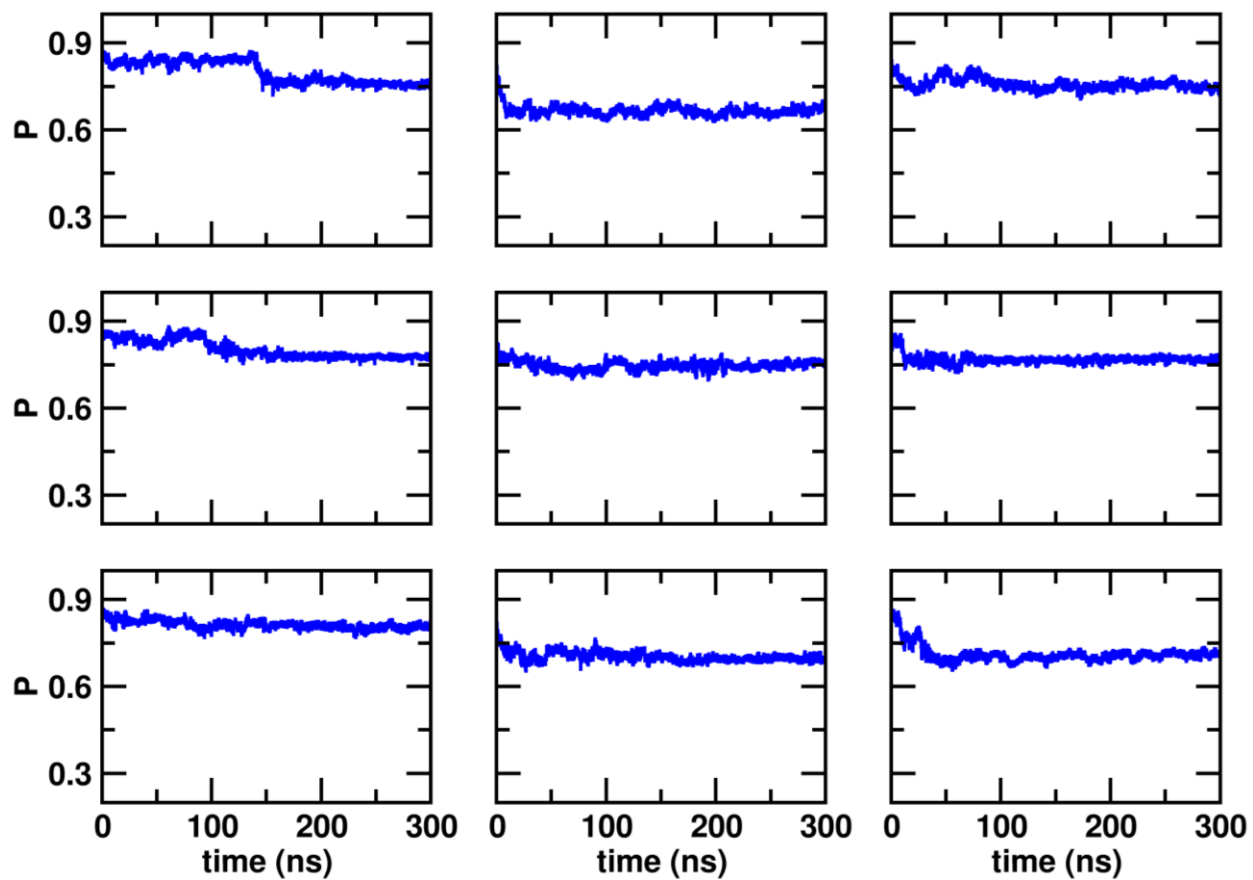


Figure S8. Time evolution of structural persistence, P , for three independent trajectories of glycosylated oligomeric trimer systems.

System	trajectory1			trajectory2			trajectory3		
	<i>pep 1</i>	<i>pep 2</i>	<i>pep 3</i>	<i>pep 1</i>	<i>pep 2</i>	<i>pep 3</i>	<i>pep 1</i>	<i>pep 2</i>	<i>pep 3</i>
<i>Unglycated</i> <i>trimer</i>	0.75 (0.01)	0.72 (0.01)	0.78 (0.02)	0.78 (0.01)	0.78 (0.01)	0.82 (0.02)	0.72 (0.02)	0.77 (0.01)	0.79 (0.02)
<i>Glycated</i> <i>trimer</i>	0.76 (0.02)	0.66 (0.02)	0.75 (0.02)	0.78 (0.01)	0.75 (0.02)	0.77 (0.01)	0.81 (0.01)	0.69 (0.01)	0.71 (0.01)

Table S3. Mean values of structural persistence, P , of the unglycated and glycated oligomeric trimer system averaged over last 150 ns of each trajectory. Standard deviations are provided within braces.

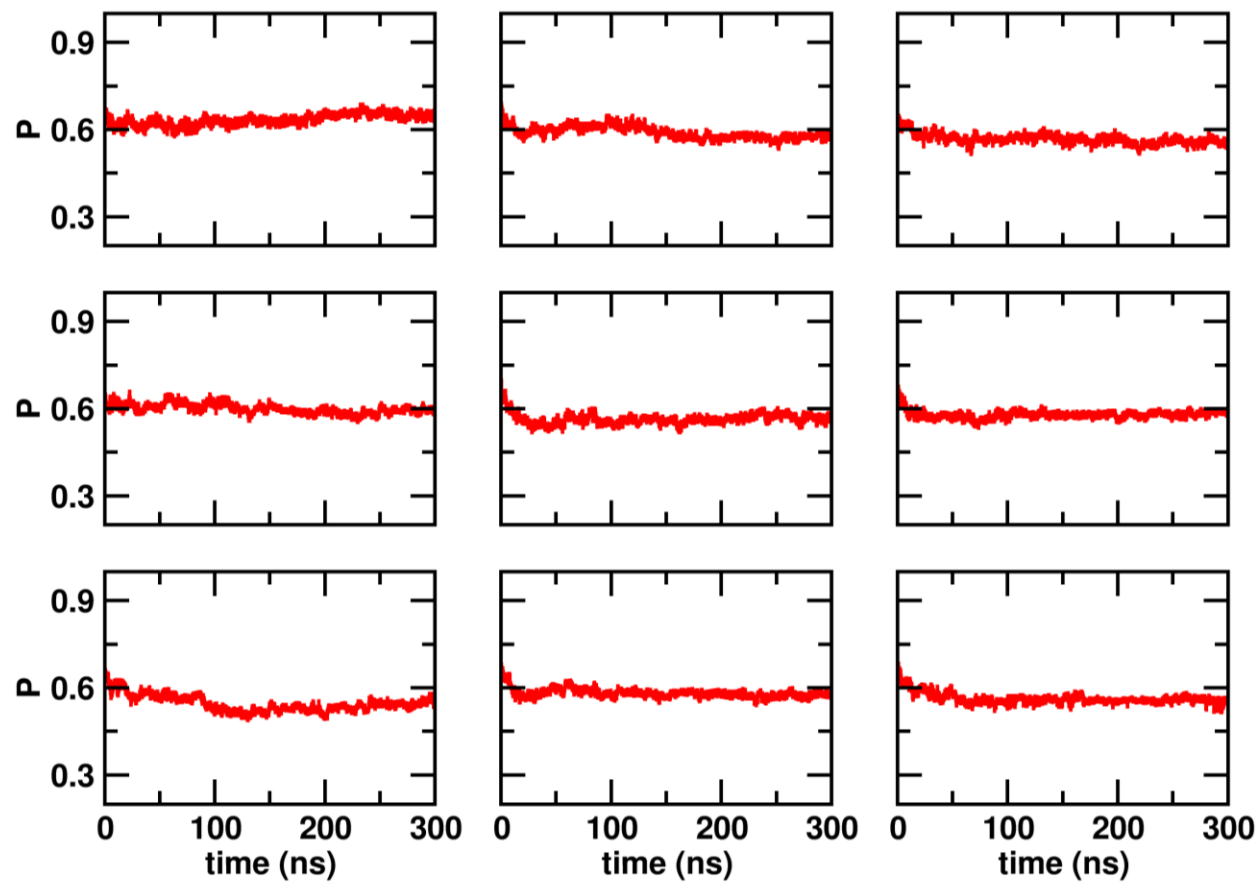


Figure S9. Time evolution of structural persistence, P , for three independent trajectories of the unglycated protofibrillar systems.

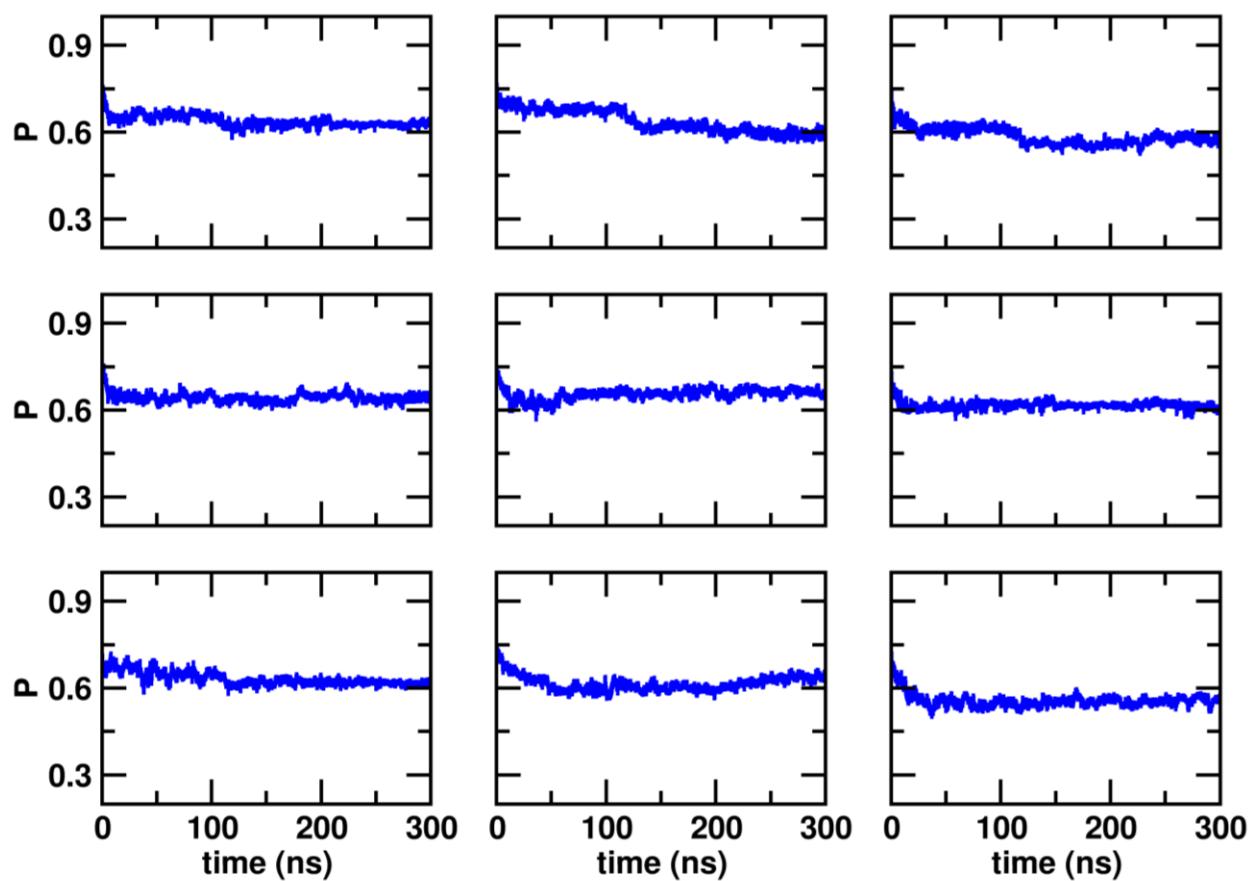


Figure S10. Time evolution of structural persistence, P , for three independent trajectories of the glycated protofibrillar systems.

<i>System</i>	<i>trajectory1</i>			<i>trajectory2</i>			<i>trajectory3</i>		
	<i>pep 1</i>	<i>pep 2</i>	<i>pep 3</i>	<i>pep 1</i>	<i>pep 2</i>	<i>pep 3</i>	<i>pep 1</i>	<i>pep 2</i>	<i>pep 3</i>
<i>Unglycated protofibrillar</i>	0.65 (0.02)	0.57 (0.02)	0.56 (0.02)	0.59 (0.01)	0.57 (0.02)	0.58 (0.01)	0.53 (0.02)	0.58 (0.01)	0.56 (0.01)
<i>Glycated protofibrillar</i>	0.63 (0.01)	0.6 (0.02)	0.57 (0.02)	0.64 (0.02)	0.66 (0.02)	0.61 (0.01)	0.62 (0.01)	0.62 (0.02)	0.55 (0.02)

Table S4: Mean values of structural persistence (P) of unglycated and glycated protofibrillar systems averaged over the last 150 ns of each trajectory. Standard deviations are provided within braces.

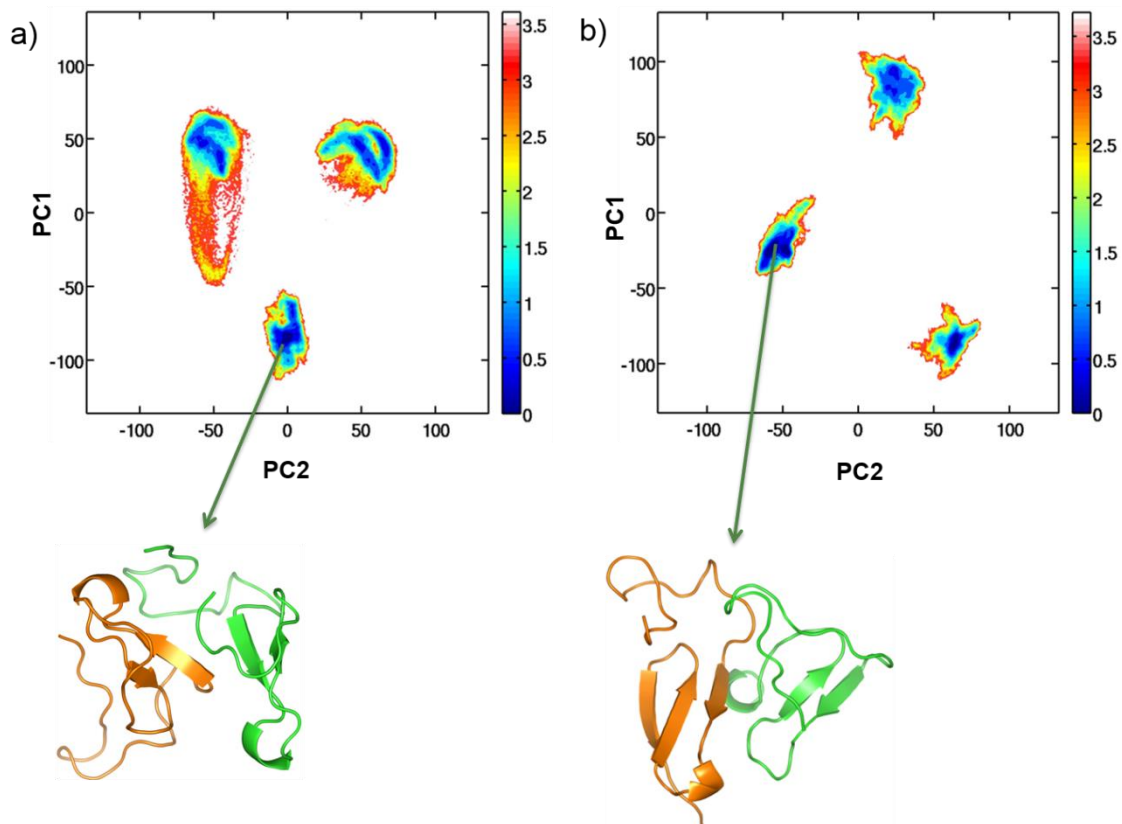


Figure S11. The pc1 vs. pc2 landscape of the a) unglycated, and b) glycosylated oligomeric dimer. Representative conformations from the most populated cluster are shown.

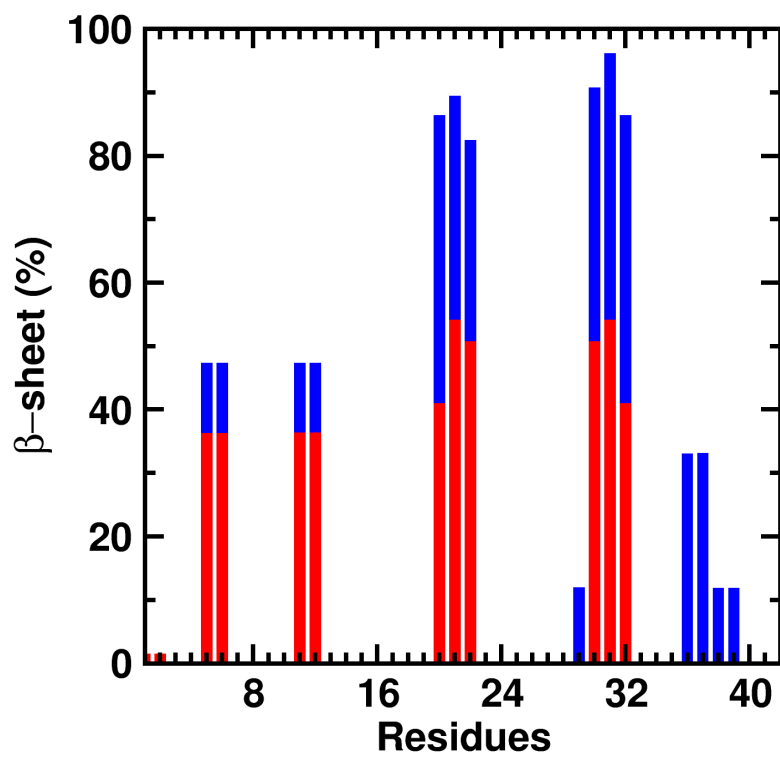


Figure S12. Comparison of the residue-wise β -sheet percentages for the most populated clusters of the unglycated (in red) and glycated (in blue) oligomeric dimer.

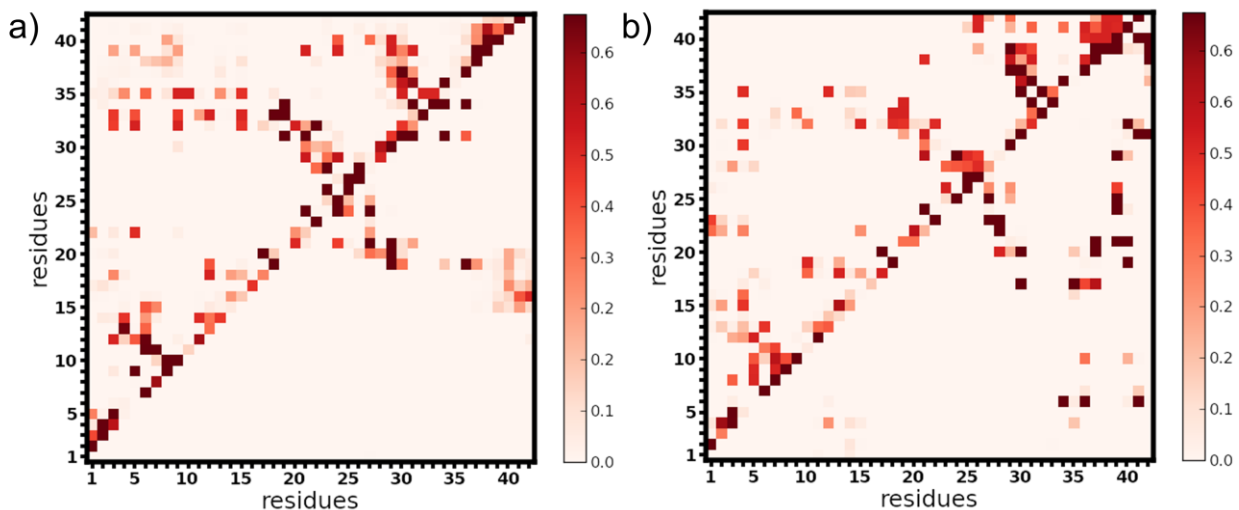


Figure S13. Residue-residue contact probabilities for a) unglycated and b) glycosylated oligomeric dimer. In the contact maps, the lower triangles display probabilities of inter-residue sidechain-sidechain contacts, while the upper triangles display probabilities of intra-residue sidechain-sidechain contacts. The probabilities along the diagonal represent the inter-peptide contacts.

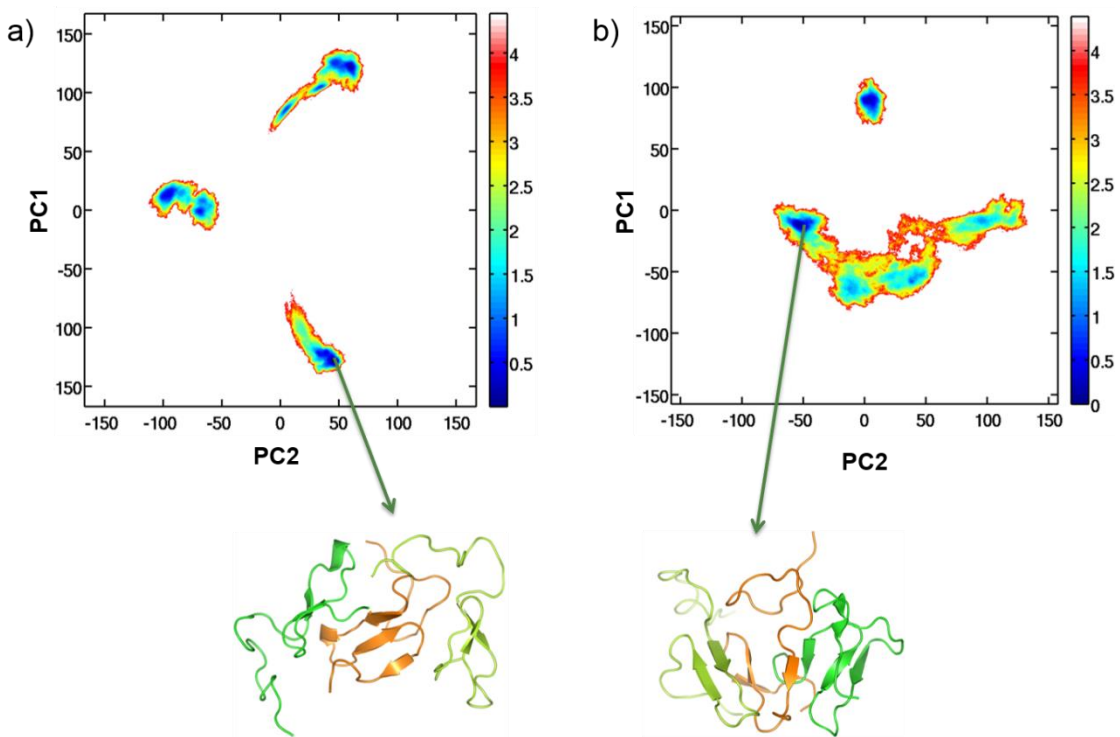


Figure S14. The pc1 vs. pc2 landscape of the a) unglycated, and b) glycated oligomeric trimer. The representative conformation from the most populated cluster is shown.

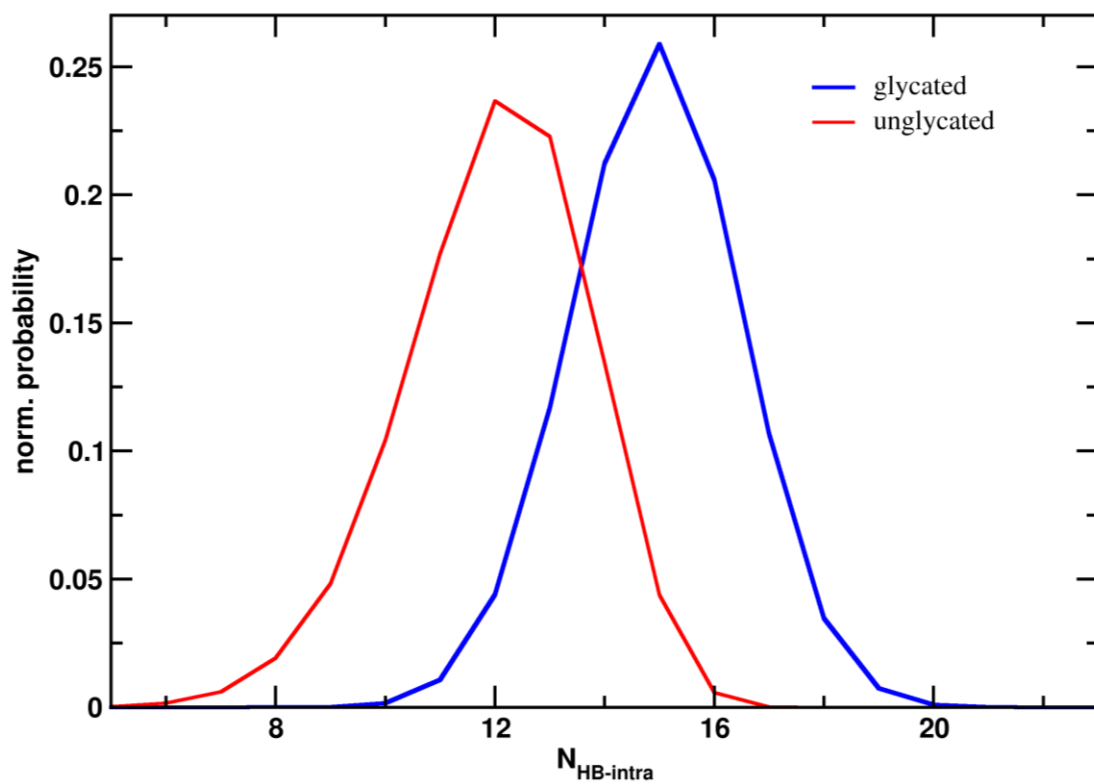


Figure S15. Normalized distribution of the number of intra-peptide backbone hydrogen bonds ($N_{HB-intra}$) between beta-sheet regions, in the unglycated and glycated oligomeric trimer systems.

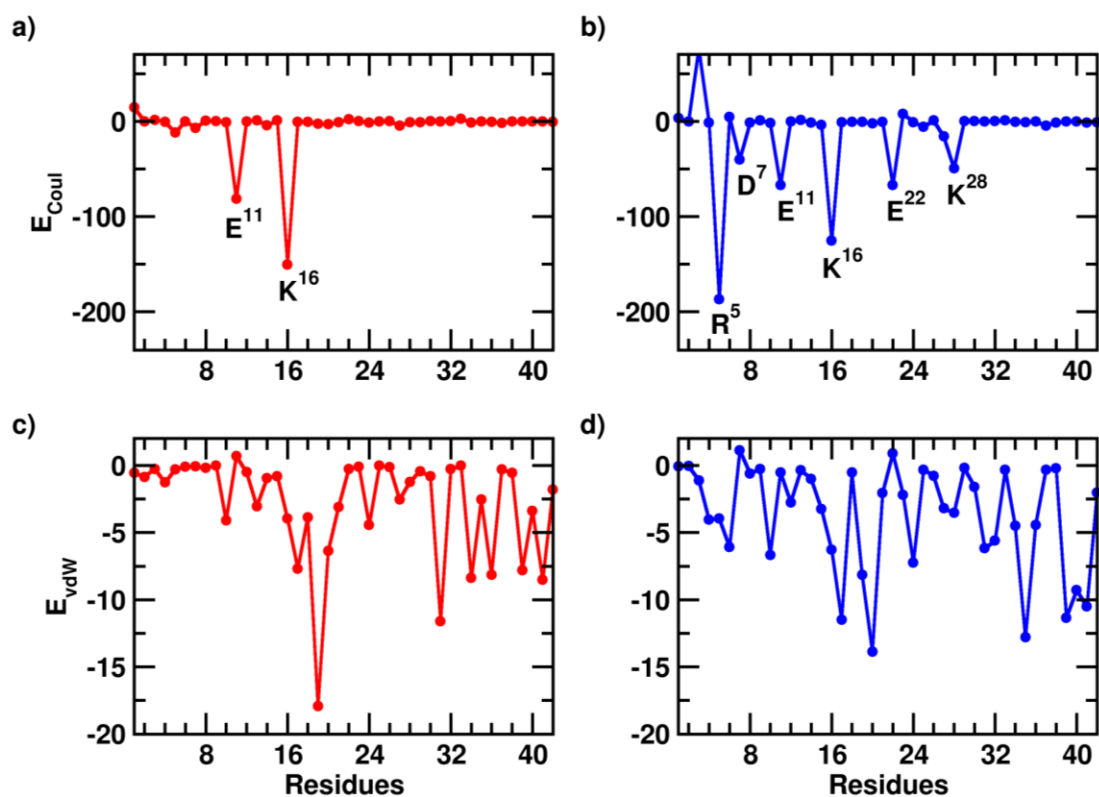


Figure S16. Residue-wise average electrostatic (upper row) and van der Waals (lower row) component of total inter-peptide interaction energies (in kcal mol⁻¹) of unglycated (in red) and glycosylated (in blue) oligomeric trimer. The residues with strong interactions are denoted with one letter code of the respective amino acids.

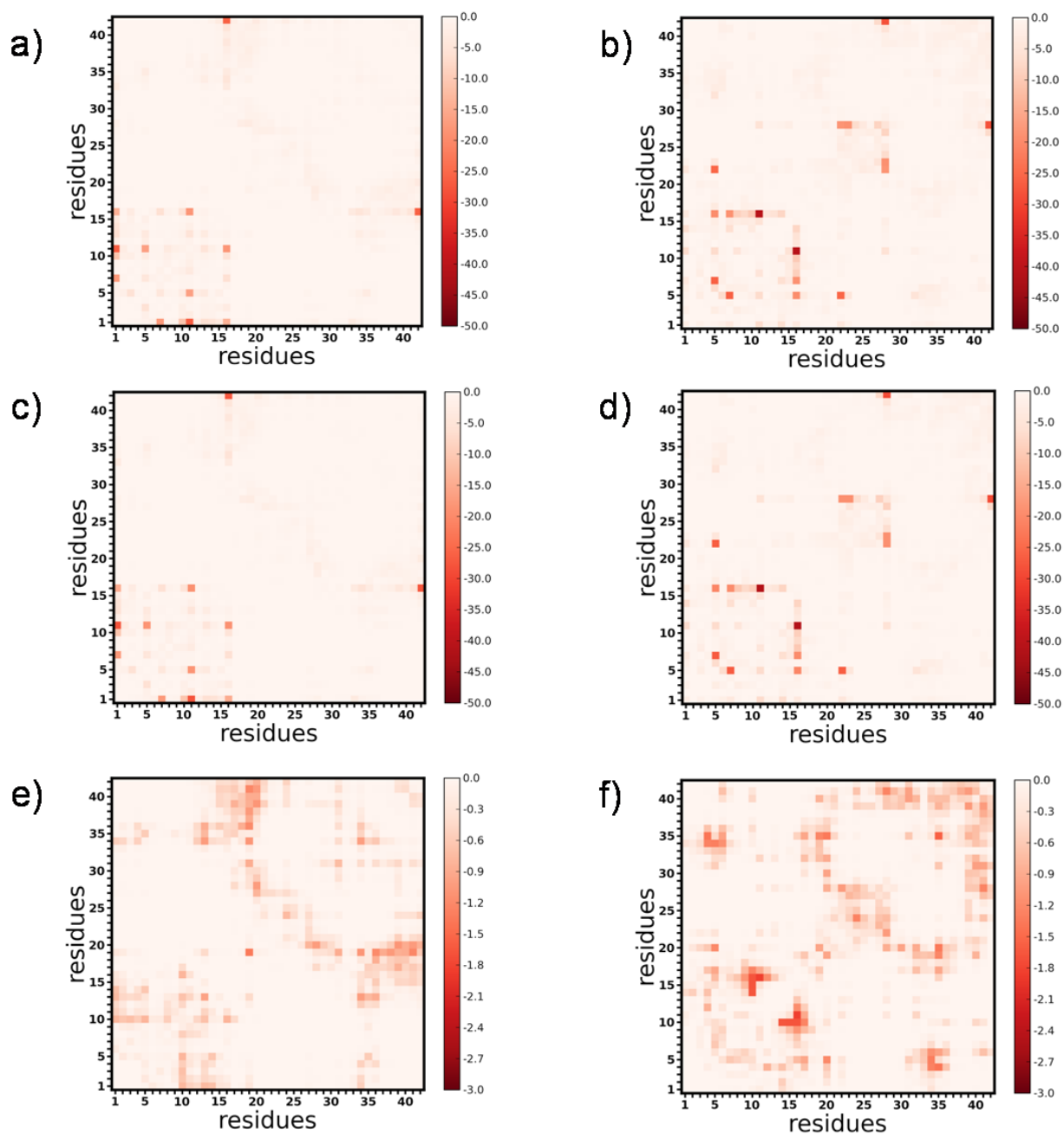


Figure S17. Residue specific inter-monomer maximum non-bonded interaction energies (in kcal mol⁻¹) of unglycated and glycated oligomeric trimers, in left- and right- columns, respectively. The total non-bonded interaction is depicted in a) and b); the electrostatic component of the total energy is depicted in c) and d); and the van der Waals component of the total energy is depicted in e) and f).

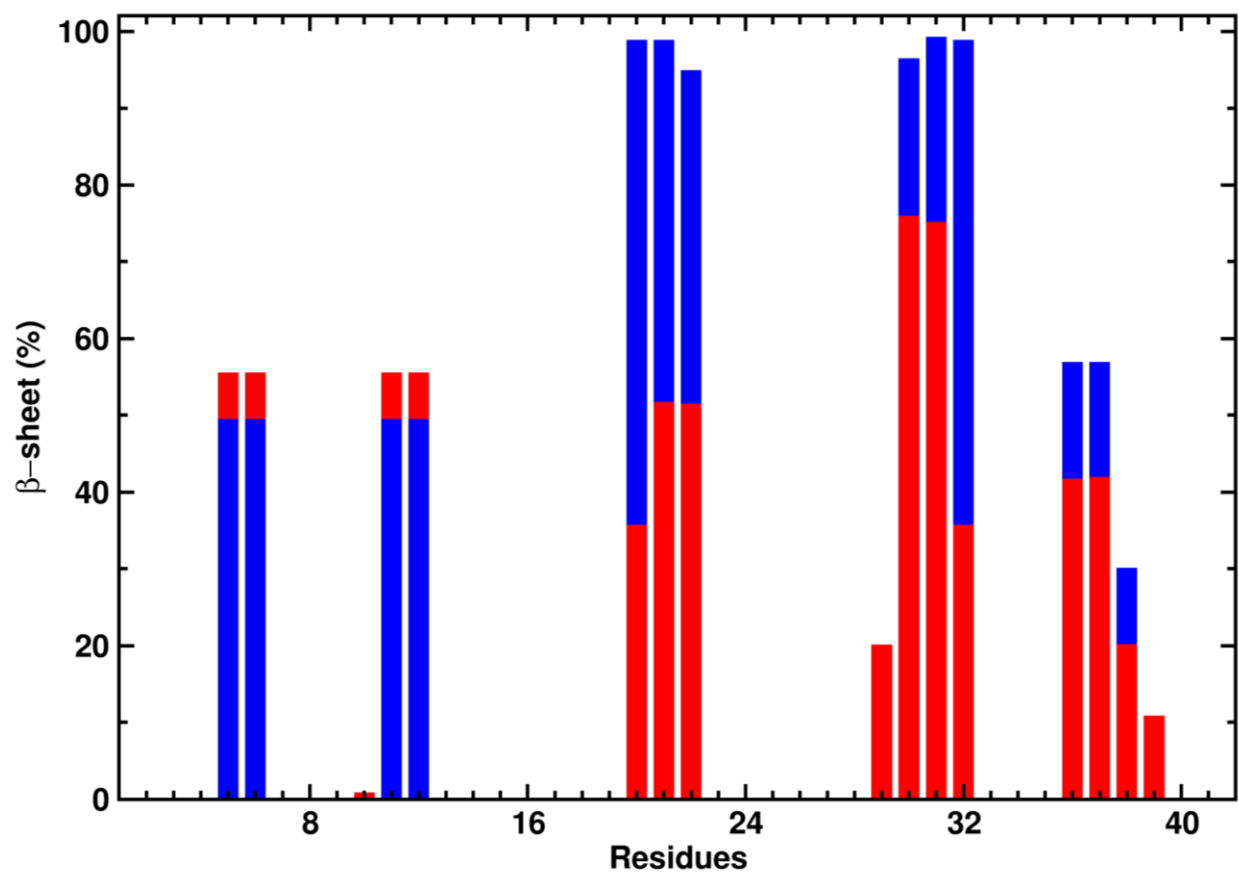


Figure S18. Residue-wise β -sheet percentages for second most populated cluster of unglycated (in red) and glycosylated (in blue) oligomeric trimer.

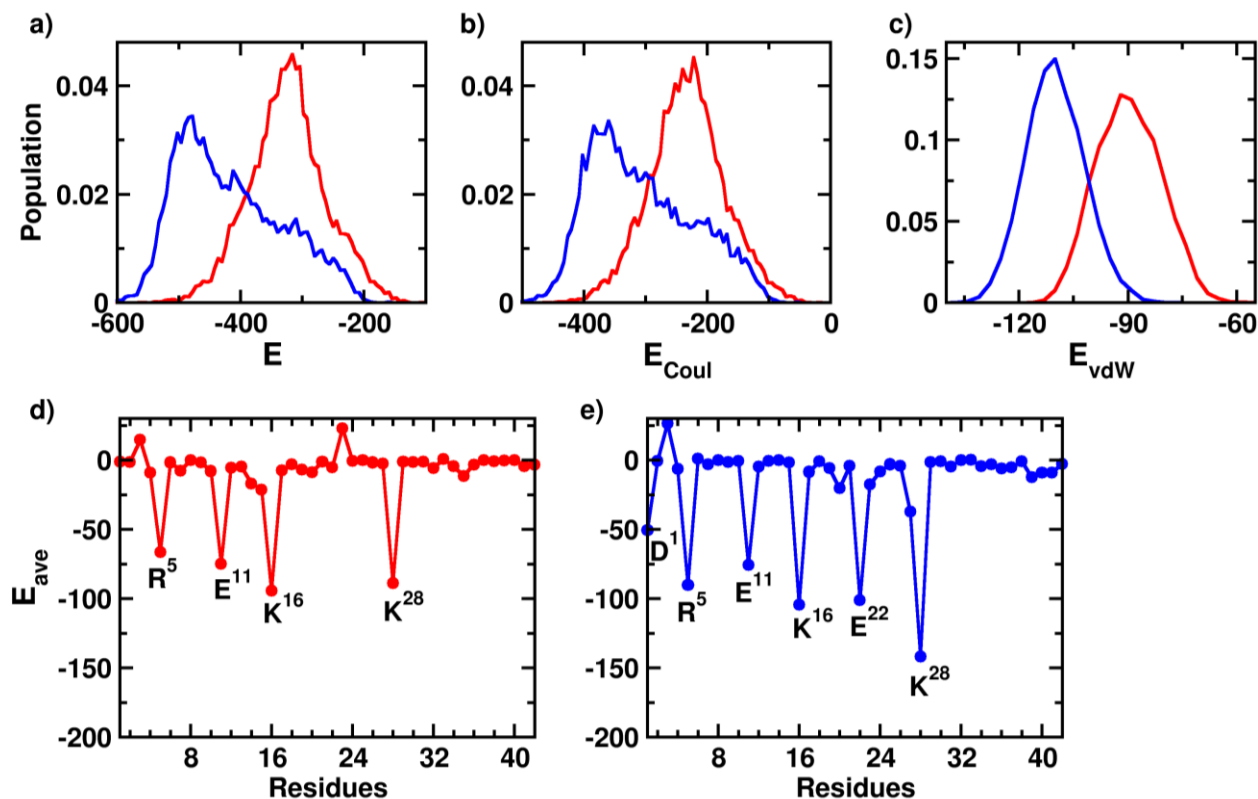


Figure S19. Distributions of inter-monomer a) non-bonded (E), b) electrostatic (E_{Coul}), and c) van der Waals (E_{vdW}) interaction energies for the second most populated cluster of unglycated (in red) and glycyated (in blue) oligomeric trimer. Residue-wise average non-bonded interaction energy (E_{ave}) for d) unglycated, and e) glycyated systems. The residues with strong interactions are denoted with one letter code of respective amino acids. All energies are in kcal mol⁻¹ unit.

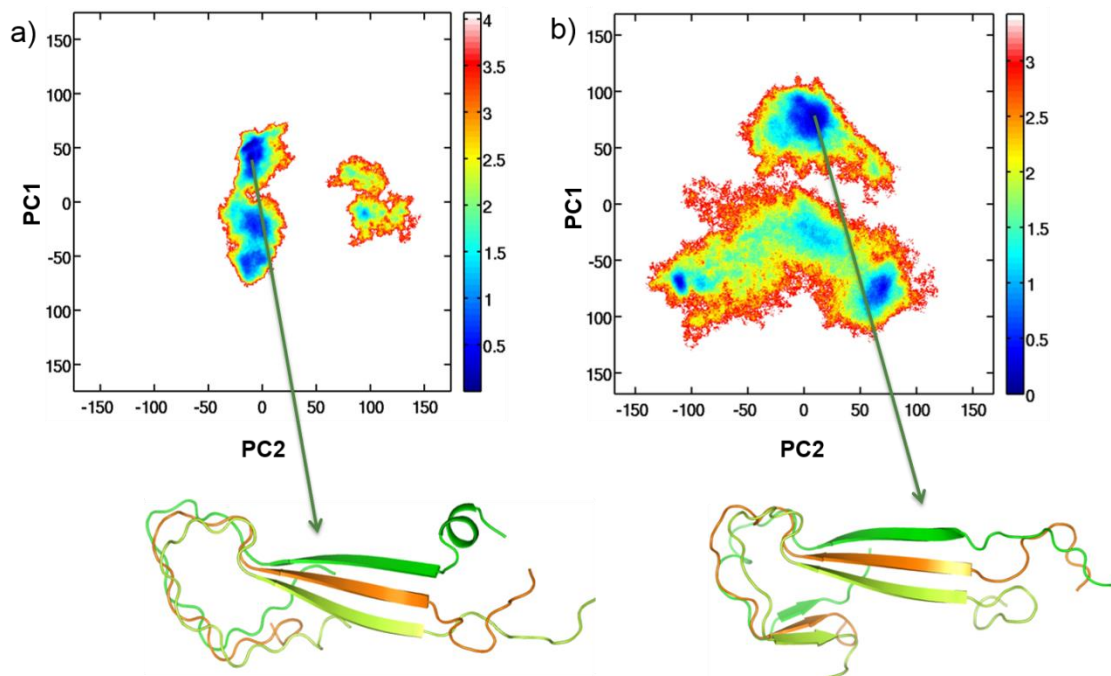


Figure S20. The pc1 vs. pc2 landscape of the a) unglycated, and b) glycated protofibrillar structure. Representative conformation from the most populated cluster is also shown.

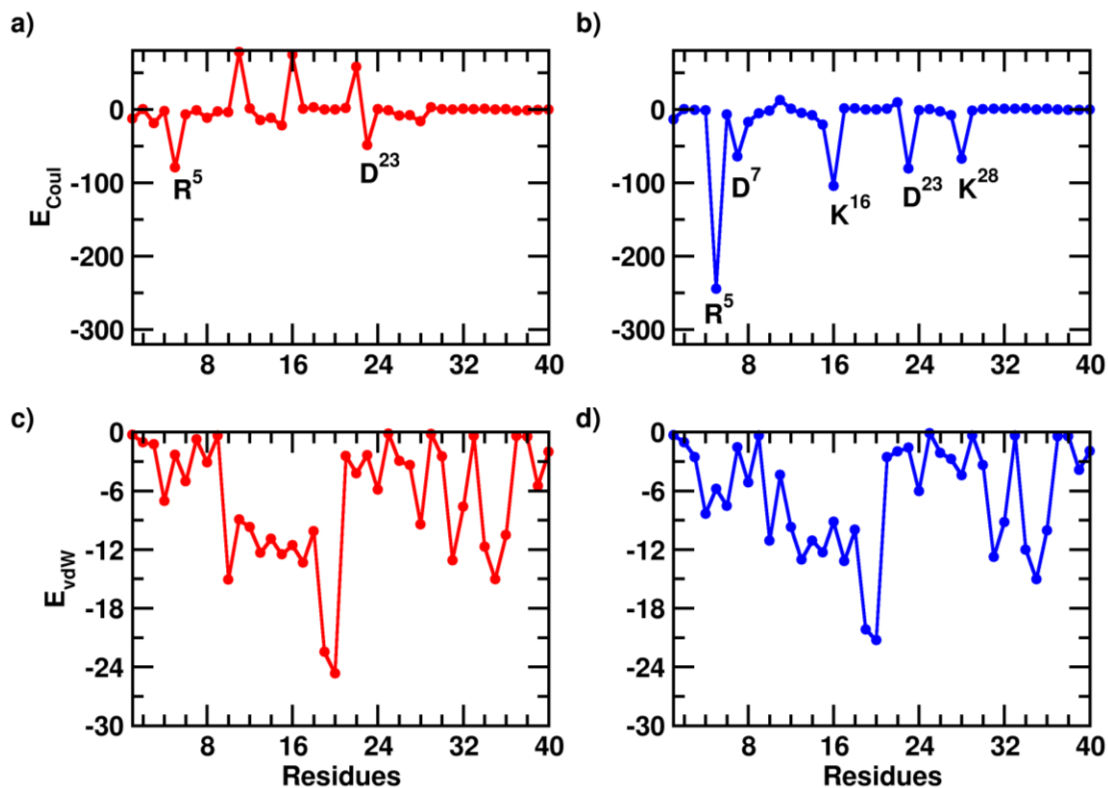


Figure S21. Residue-wise average electrostatic (upper row) and van der Waals (lower row) component of total inter-peptide interaction energies (in kcal mol⁻¹) of unglycated (in red) and glycated (in blue) Aβ protofibrils. The residues with strong interactions are denoted with one letter code of respective amino acids.

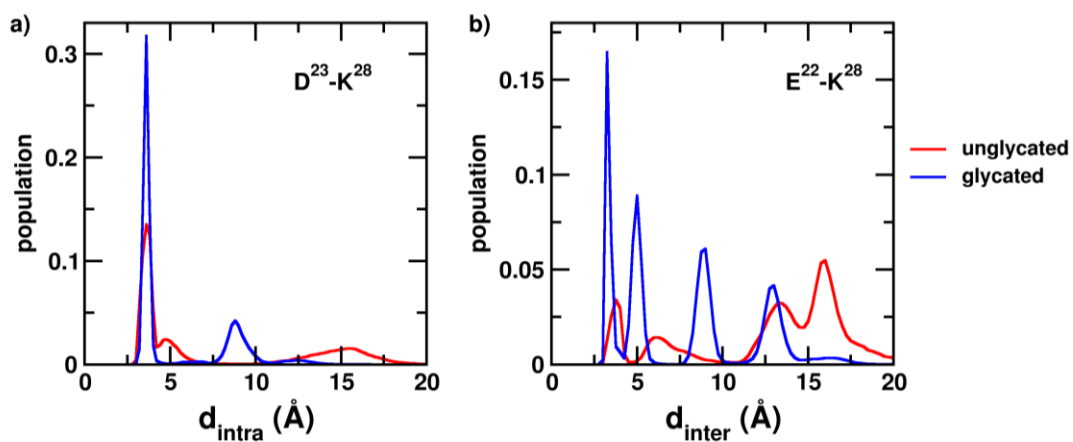


Figure S22. Distribution of intra- (d_{intra}) and inter-peptide (d_{inter}) distances between the salt-bridge forming pairs in turn region of unglycated and glycated A β protofibrillar structure.

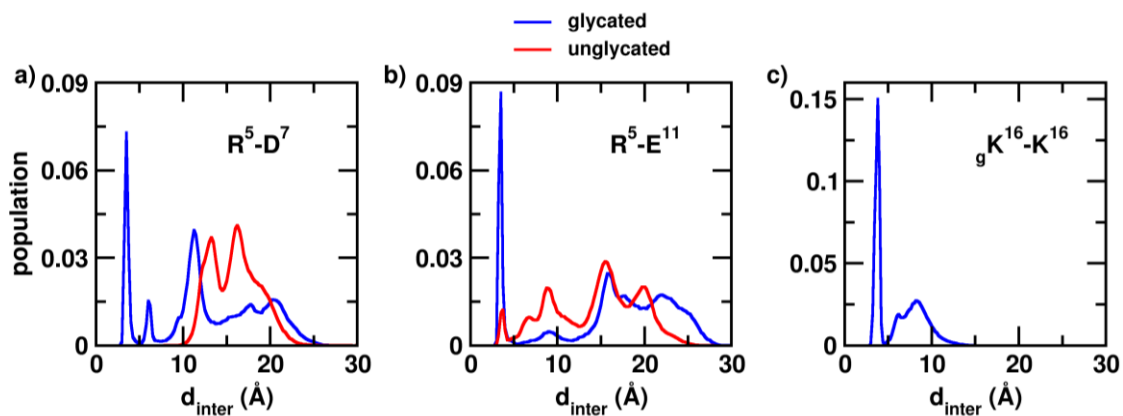


Figure S23. Distribution of inter-peptide (d_{inter}) distances between the salt-bridge forming pairs in N-terminal region of unglycated and glycated A β protofibrillar structure.

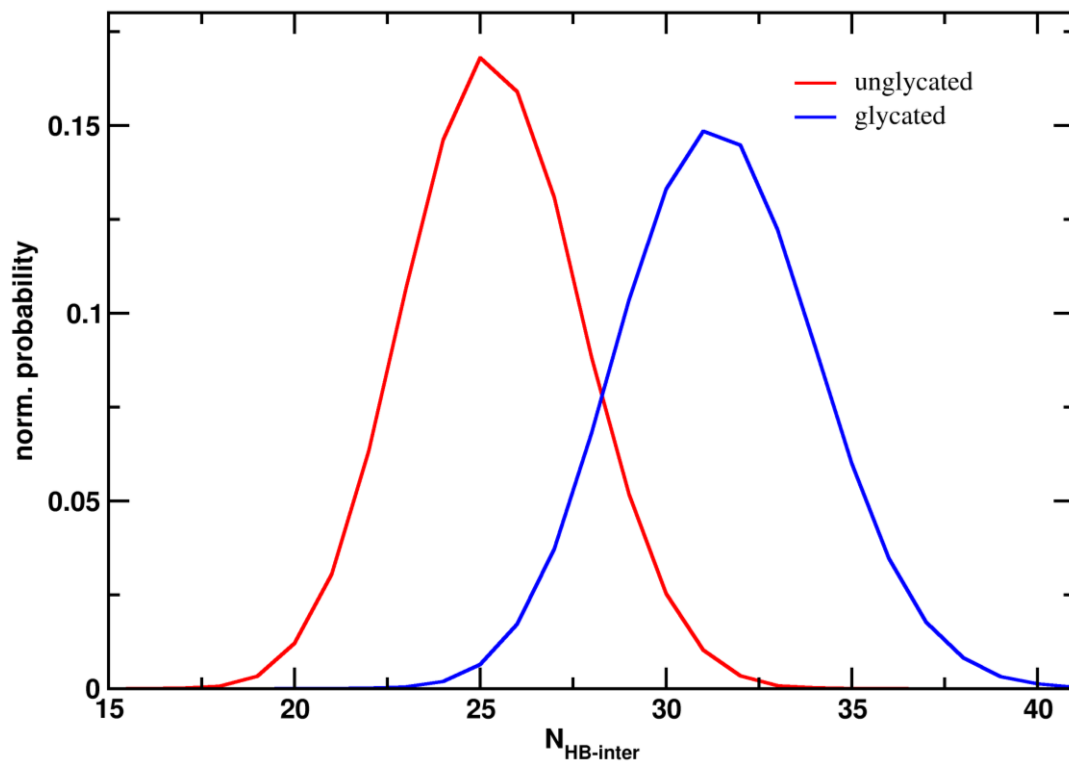


Figure S24. Normalized distribution of the number of inter-peptide backbone hydrogen bonds ($N_{HB-inter}$) between the beta-sheet regions in the unglycated and glycated protofibrillar system.

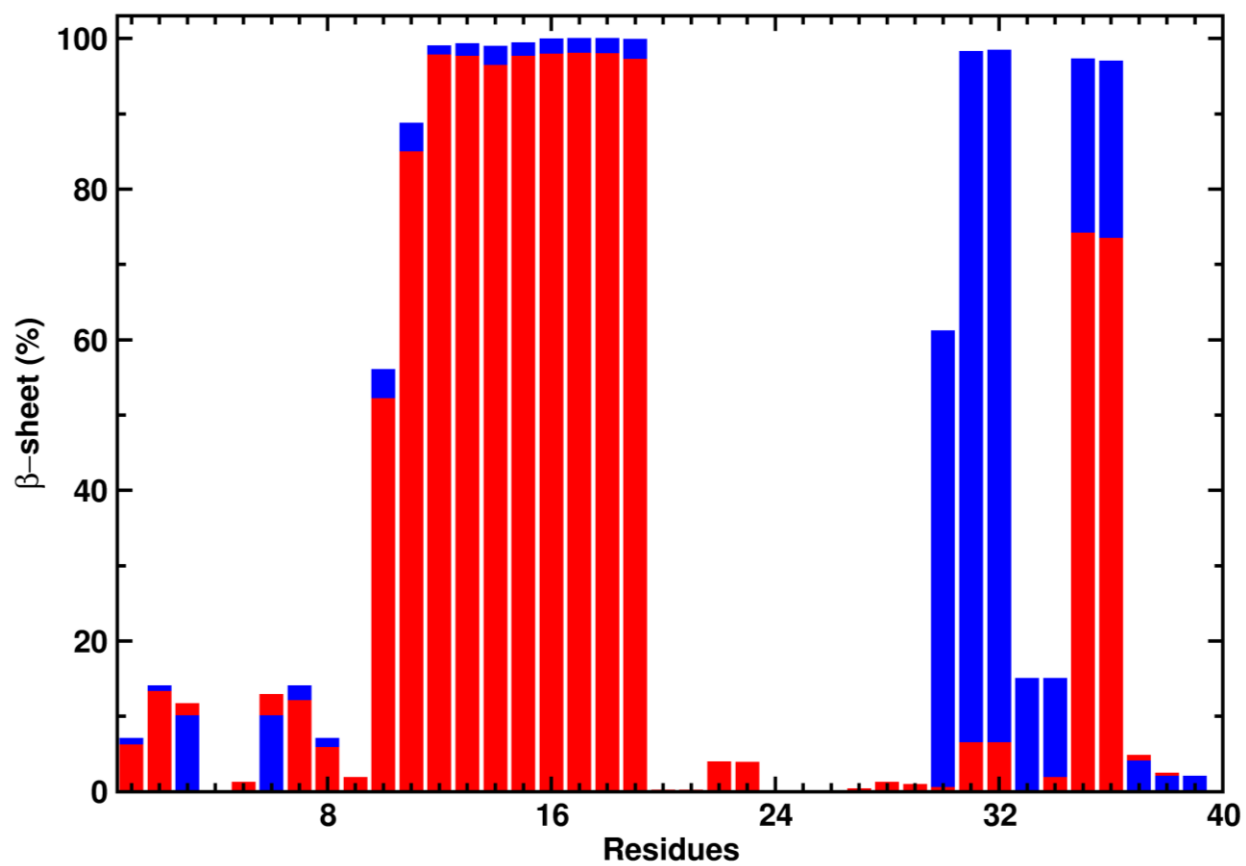


Figure S25. Residue-wise β -sheet percentages for the second most populated cluster of unglycated (in red) and glycated (in blue) A β protofibrillar system.

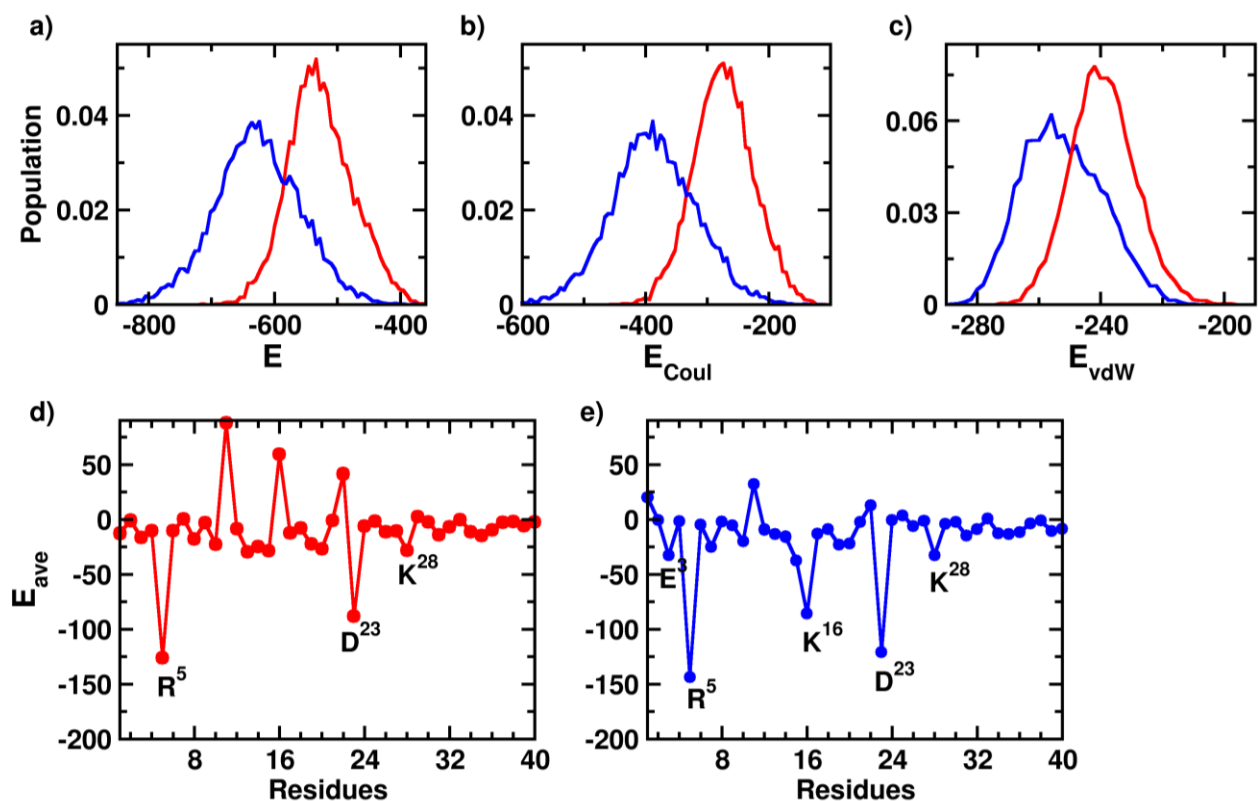


Figure S26. Distribution of inter-monomer a) non-bonded (E), b) electrostatic (E_{Coul}), and c) van der Waals (E_{vdW}) interaction energy for second most populated cluster of unglycated (in red) and glycosylated (in blue) Aβ protofibrillar system. Residue-wise average non-bonded interaction energy (E_{ave}) for d) unglycated and e) glycosylated system. The residues with strong interactions are denoted with one letter code of respective amino acids. All energies are in kcal mol⁻¹ unit.

References:

1. P. Chatterjee and N. Sengupta, *Eur. Biophys. J.*, 2012, **41**, 483-489.
2. P. Chatterjee and N. Sengupta, *Mol. BioSyst.*, 2016, **12**, 1139-1150.
3. P. Chatterjee, S. Bagchi and N. Sengupta, *J. Chem. Phys.*, 2014, **141**, 205103.