O-Glycosylation enhances the conformational landscape of self-assembling peptides

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Glycosylation is a common biological post-synthetic modification significant, yet under-explored implications for enhancing functionality in designed supramolecular materials. In this work, we use simple self-assembling tripeptides containing polar amino acids Ser and Thr as sites for glycosylation. Striking observations from the computational modeling of these systems show that the conformational landscape of these simple tripeptides, typically pre-organized by Phe-Phe self-stacking interactions, is dramatically increased by glycosylation. This is underpinned by the generation of a diverse supramolecular interactome consisting of contributions from weaker interactions such as CH-π. We also find striking and counter-intuitive differences between the two-polar amino acids studied, with the more hydrophobic Thr residue causing an overall reduction in aggregation propensity due to disruption of Phe/Phe hydrophobic collapse driven self-assembly by CH-π interactions. The glycosylation leads to increase in overall hydration of these peptides which is reflected in the changes in material properties such reduced formation of amyloid-like structures and enhanced thermostability. Therefore, we believe this to be a first step in understanding the changes in molecular interactions upon glycosylation and their implications in the design of self-assembling glycopeptide-based materials.