

Title: Molecular Dynamics Insights into the Co-Assembly of Riboflavin with Tryptophan-Containing Tripeptides for Vitamin Protection

Project Authors: Max Zeldich^{1,2,3}, Paola Colon de Leon³, Maeva Coste³, Hamish Swanson³, Rein Ulijn^{2,3}

1) Macaulay Honors College, City University of New York, NY

2) Department of Chemistry, Hunter College, City University of New York, New York, NY

3) Nanoscience Initiative, Advanced Science Research Center, Graduate Center, City University of New York, New York, NY

Riboflavin (RFVR), also known as vitamin B₂, is a poorly water-soluble compound found in a variety of food products and supplements and is essential to human health¹. However, RFVR is a fragile molecule that is highly susceptible to degradation from environmental factors, particularly visible and ultraviolet light¹. Short peptides have emerged as a promising strategy for protecting such compounds, owing to their ability to co-assemble with other molecules into a wide range of nanostructures, depending on their amino acid composition². Molecular dynamics (MD) simulations are a powerful tool for studying co-assembly, as they allow direct probing of intermolecular interactions and compound conformations². As part of a larger project combining computational and experimental approaches, this work presents the computational investigation of whether two tryptophan-containing tripeptides, WKY (tryptophan-lysine-tyrosine) and WYK (tryptophan-tyrosine-lysine), can co-assemble with RFVR with the goal of preventing its degradation. We performed MD simulations of mixed WKY/RFVR and WYK/RFVR systems to characterize their interactions and co-assembly behavior. Single-component control simulations of WKY, WYK, and RFVR alone served as baselines for comparison with the mixed systems. We quantified the solvent-accessible surface area (SASA), the dispersion of RFVR molecules, hydrogen bond counts, π -stacking interactions, and tripeptide sidechain torsion angles to identify the drivers of the observed behavior. Compared with the RFVR-only control, both tripeptides co-assembled with RFVR and prevented its aggregation with itself. Significant π -interactions between the tryptophan residues of the tripeptides and the flavin moiety of RFVR, together with hydrogen bonding between the components, emerged as the primary drivers of this behavior. These computational findings correlate with complementary wet lab results, in which WKY and WYK protected RFVR from visible and ultraviolet light degradation. Together, these results suggest that short-peptide co-assembly is a promising strategy for protecting vitamins from light-driven damage and may inform the design of peptide-based protective formulations.

References: 1) Sheraz, M. A., Kazi, S. H., Ahmed, S., Anwar, Z., & Ahmad, I. (2014). Photo, thermal and chemical degradation of riboflavin. *Beilstein J. Org. Chem.*, 10, 1999–2012.

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