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# Molecular-Level Insights into Multi-Component Peptide Assembly by NMR

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Natural supramolecular systems are rarely composed of a single molecular component. Biological structures and functions instead emerge from the coordinated interactions of multiple molecules with different chemical identities, interaction motifs, and assembly preferences. Understanding how such components recognize one another, associate, and select specific assembly pathways is therefore essential for deciphering complex biological organization and for designing synthetic multicomponent materials.

Multi-component peptide systems provide a particularly versatile platform for addressing these questions. Depending on sequence compatibility, solvent environment, and preparation pathway, different peptide components may cooperatively co-assemble, self-sort, or interfere with each other's assembly.[1] However, it remains unclear what determines which of these outcomes is selected.

To address this question, nuclear magnetic resonance (NMR) spectroscopy is used as a central analytical platform to follow two peptides with distinct assembly preferences from soluble and pre-associated states to supramolecular assemblies. Because peptide interactions are encoded by amino-acid sequence, identifying which residues and functional groups respond during association is essential for understanding how sequence directs assembly.[2] Through residue-specific analyses, the molecular sites that participate in or respond to peptide–peptide interactions can be pinpointed, while complementary analytical methods provide additional structural and thermodynamic information.

The results show that weak, residue-specific peptide interactions can occur before aqueous assembly. Through-space NMR correlations revealed close contacts between specific side-chain regions, while selected residues near charged groups showed pronounced sensitivity to the local environment. Upon transfer to aqueous conditions, the presence of a second peptide caused stronger line broadening and signal intensity loss, indicating reduced molecular mobility and a larger fraction of peptide entering NMR-invisible assembled states. Importantly, premixing the peptides before assembly and adding one peptide to pre-assembled structures produced distinct signal intensities and temperature-dependent responses, showing that the timing of the first molecular encounter influences the resulting assembly state.

Together, these findings show that multi-component peptide assembly cannot be explained solely by the final structures formed. Instead, early molecular recognition, solvent-sensitive pre-association, and pathway dependence all contribute to the resulting assembly state. More broadly, this work demonstrates how NMR can identify the molecular sites involved in peptide association and connect early interactions with subsequent supramolecular assembly.

[1] S. Fleming, *et al.*, *Biomacromolecules* **15**, 4, 1171 (2014)
[2] K. Kaygisiz *et al.*, *Nature Reviews Materials* **10**, 449 (2025)