Hydrogel formation via base-triggered conversion of a peptide progelator

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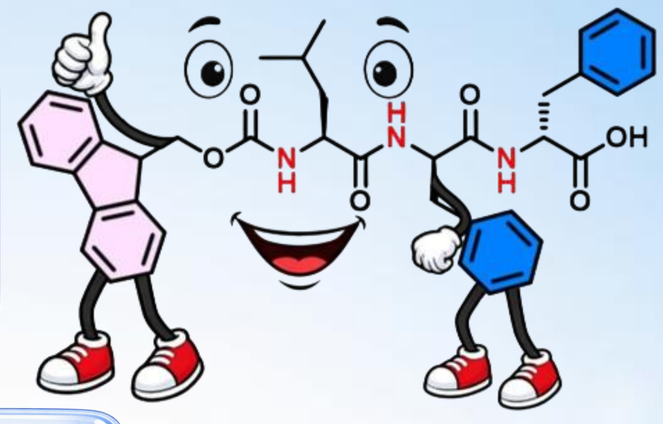
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INTRODUCTION

Short peptides are promising low molecular weight gelators (LMWGs) due to their biocompatibility and structural versatility, although controlling their gelation remains challenging. [1] Here, we present a chemically activated supramolecular hydrogel based on a heterochiral [2] tripeptide progelator (**Fmoc-L-Leu-D-Phe-D-Phe**), enabling spatiotemporal control over gel formation and generating architectures different from conventional pH-triggered systems. [3]

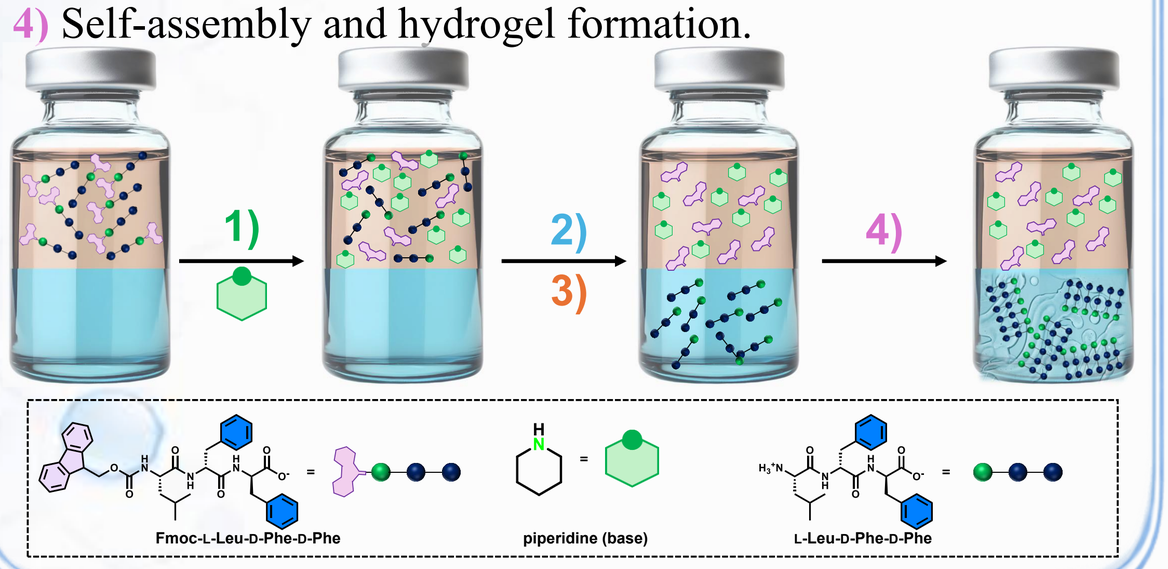
Fmoc-L-Leu-D-Phe-D-Phe



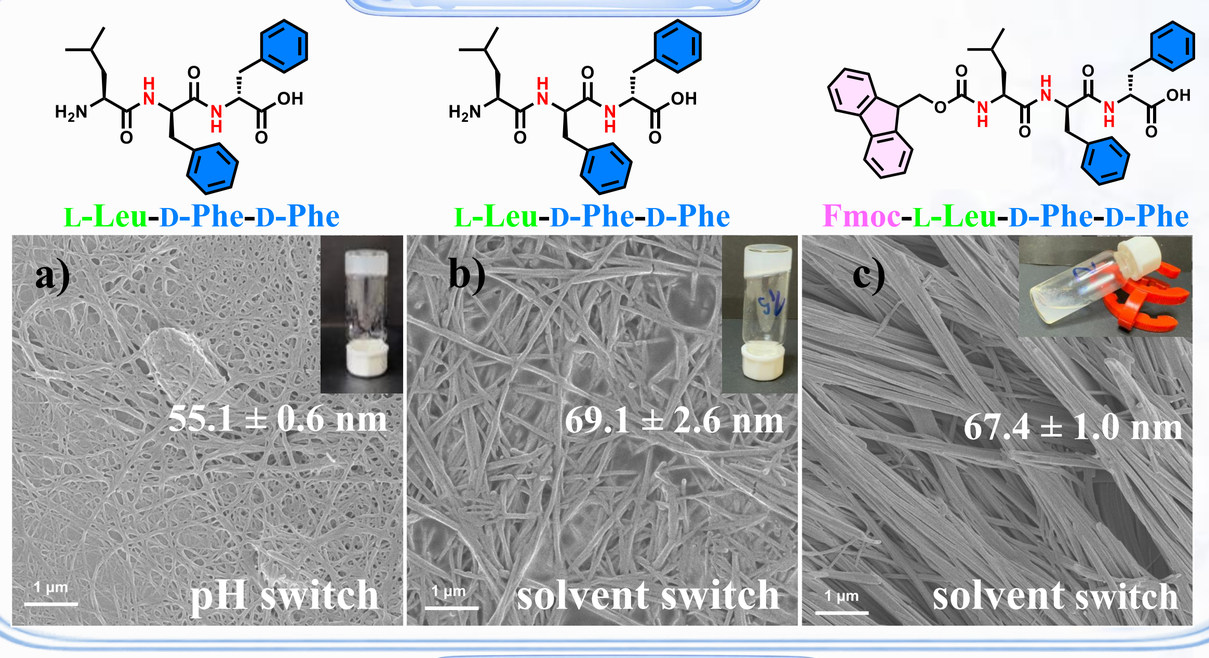
RESULTS AND DISCUSSION

Experimental setup

1) Biphasic system: ethyl acetate / phosphate buffer (pH 7.4).
2) Addition of piperidine triggers Fmoc removal, generating **L-Leu-D-Phe-D-Phe**.
3) Migration of **L-Leu-D-Phe-D-Phe** to the buffer layer.
4) Self-assembly and hydrogel formation.



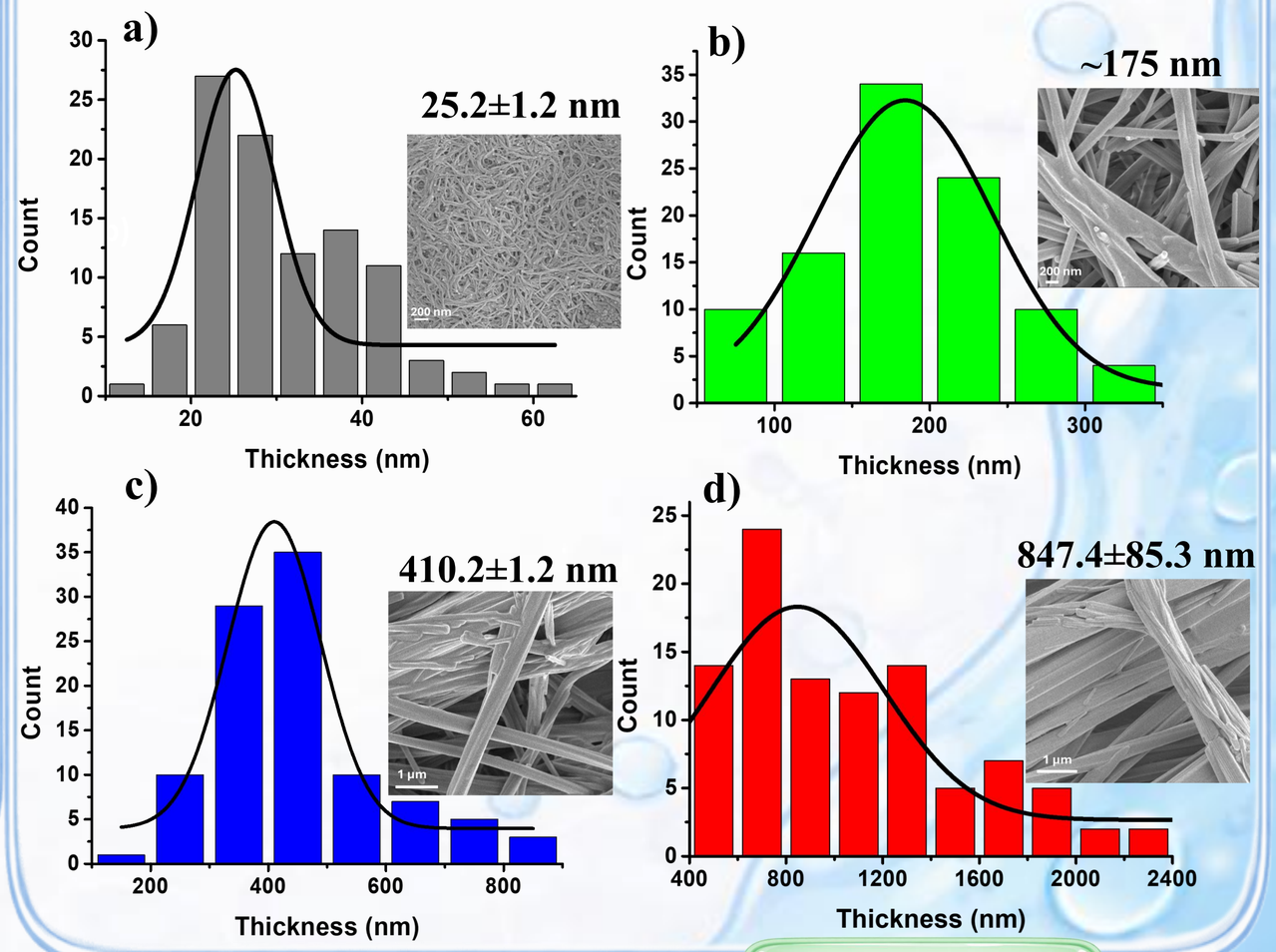
Gelation behavior



Gels morphology

- ❑ **Control (a)** ⇨ curved fibrils typical of peptide organogel.
- ❑ **1 eqs. (b)** ⇨ thicker fibrils than (**a**), due to partial Fmoc removal.
- ❑ **5 eqs. (c)** ⇨ thicker and more bundled fibrils than in (**b**).
- ❑ **10 equiv. (d)** ⇨ further increase in fiber diameter, more hetereogeneity than in (**c**).

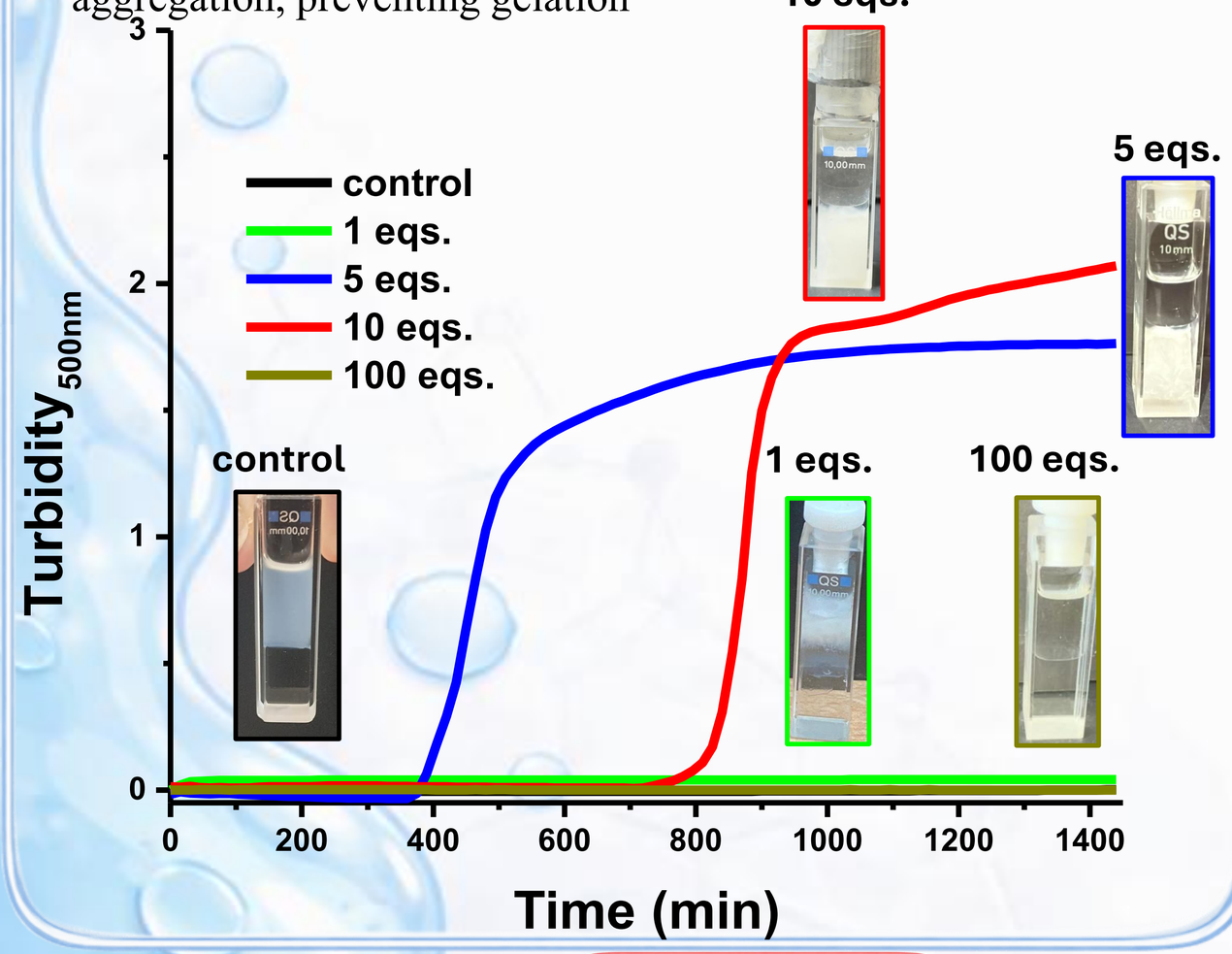
❑ **Biphasic ethyl acetate/phosphate buffer system yields significantly thicker fibrils than pH-switch assembly.**



UV-Vis kinetic studies

❑ **Turbidity** was monitored over time ⇨ evaluation of hydrogel formation with different equivalents of piperidine.

- ❑ **0–1 equivalents** ⇨ organogel formation
- ❑ **5–10 equivalents** ⇨ hydrogel formation
- ❑ **100 equivalents** ⇨ high aqueous pH suppresses peptide aggregation, preventing gelation



CONCLUSIONS

- Reaction-driven biphasic activation enables spatiotemporal control over peptide hydrogelation via in situ gelator generation.
- Hydrogelation occurs after base-mediated deprotection and peptide transport into the aqueous phase within a narrow operational window defined by kinetics, transport, and local pH.
- Distinct fibrillar morphologies reveal reaction-controlled supramolecular organization.

REFERENCES

[1] Draper, E. R.; Adams, *D. J. Chem,* **2017**, *3*, 390–410.
[2] Marchesan, S. ; *et al. Nanoscale* **2012**, *4*, 6752–6760.
[3] *10.26434/chemrxiv.15005985/v1*