Engineering Softness: How Molecular Tweaks in Coiled Coils Shape Hydrogel Behavior

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https://doi.org/10.17952/38EPS.2026.P100

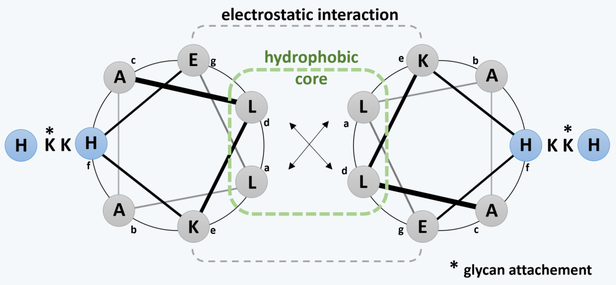
Introduction

Hydrogels are three-dimensional polymer networks that retain large amounts of water. The networks themselves are held together by different types of cross-linkages that are fine-tuned by chemical modification and external stimuli, e.g., heat, ions, or pH.[1] Hydrogels have been used in numerous biomedical and bioengineering applications, like drug-delivery systems or as soft contact lenses. [2]

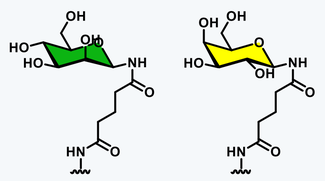
Aim

- tuning viscoelastic properties of mucin-inspired peptide hydrogels
- synthesis of a peptide scaffold suitable for metal-ion coordination
- investigating structural and viscoelastic property changes in modified peptide hydrogels

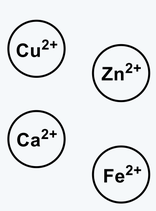
Metal-induced cross-linking



glycan attachement



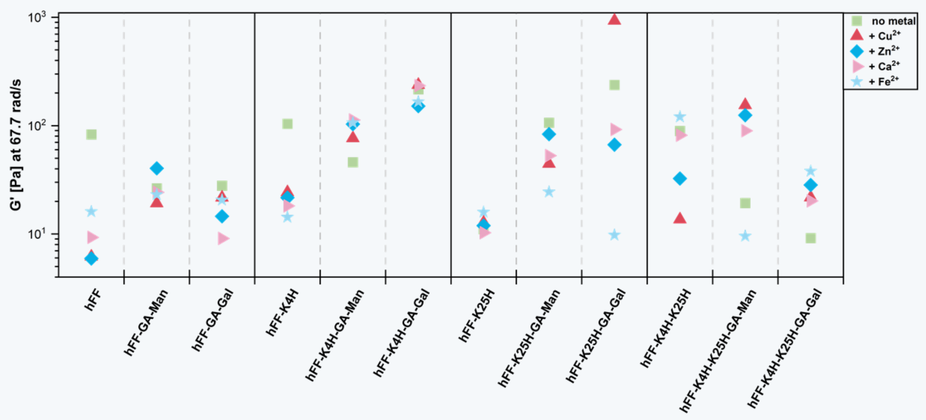
bivalent metal-ions



name	sequence
hFF-K4H	[2]-Abz-LK**H**ELAALKKELAALK**K***ELAALKKEL
hFF-K25H	[2]-Abz-LKKELAALKKELAALK**K***ELAALK**H**EL
hFF-K4H-K25H	[2]-Abz-LK**H**ELAALKKELAALK**K***ELAALK**H**EL

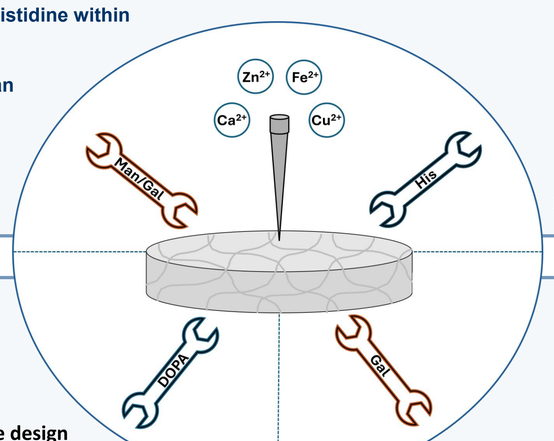
Rheological properties

conditions: c = 0.5 wt%; pH 7.4 [(glyco)-peptide: hFF-K4H-K25H at pH 7]; water; T = 37° C



Key factors:

- position of histidine within the peptide
- type of glycan
- metal(II)-ion

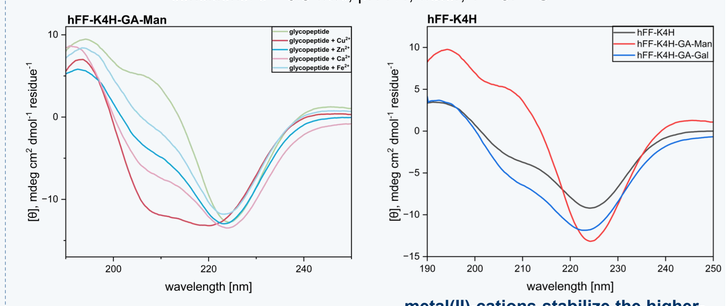


Full publication:[3]

DOI: 10.1002/psc.70059

Circular dichroism (CD)

conditions: c = 0.5 wt%; pH 7.4; water; T = 37° C

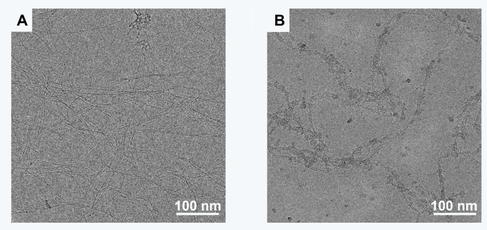


mannose-functionalized peptide adopts a higher-order structure

metal(II)-cations stabilize the higher-order structure of the non-glycosylated peptide, inducing an α-helical conformation

Cryo-TEM

conditions: c = 0.1 mM; pH 7.4; water



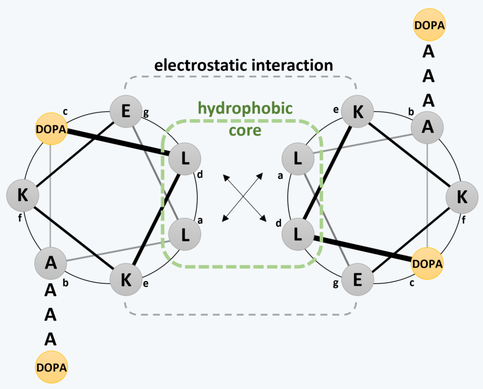
hFF03-K4H-GA-Gal

hFF03-K4H-GA-Gal + 0.25 eq. Cu2+

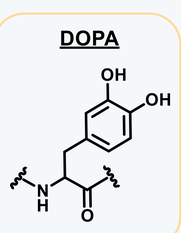
formation of long fibres without copper ions

densely packed fibre bundels after addition of 0.25 eq. copper ions

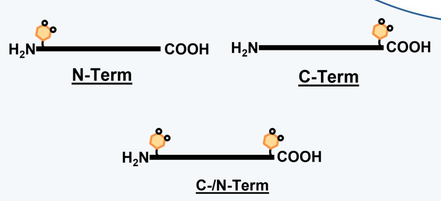
C-/N-Modifications: DOPA



DOPA



Peptide design

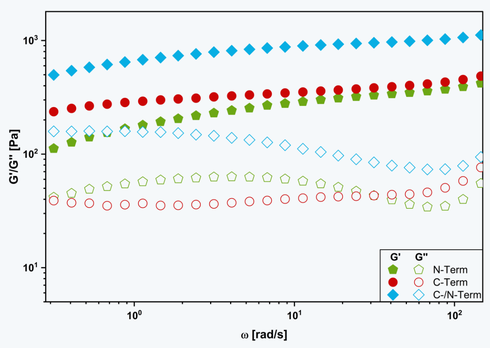


sequence:

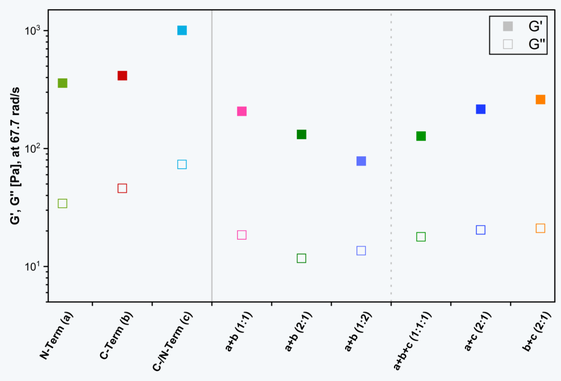
H_2N-DOPA-LKKELAALKKELAALKKELAALKKEL-DOPA-OH

Rheological properties

conditions: c = 0.5 wt%; pH 7.4; PBS ; T = 37° C



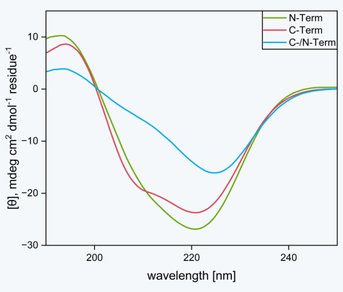
C- and N-Term DOPA-functionalized peptides show similar viscoelastic properties, whereas dual-terminal DOPA modification results in a stiffer hydrogel



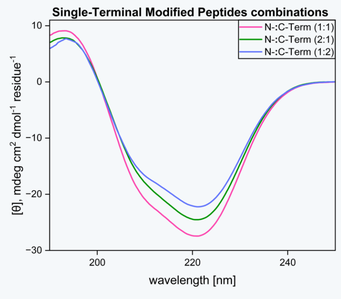
mixtures of the different DOPA-modified peptides form less stiff hydrogels compared to the pure samples

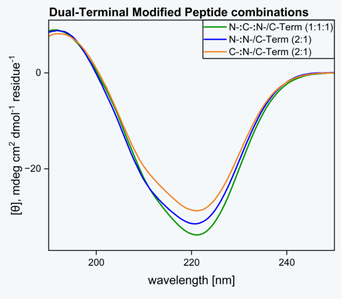
Circular dichroism (CD)

conditions: c = 0.5 wt%; pH 7.4; PBS; T = 37° C



formation of higher ordered structures from N-Term and C-/N-Term, while C-Term forms α-helix

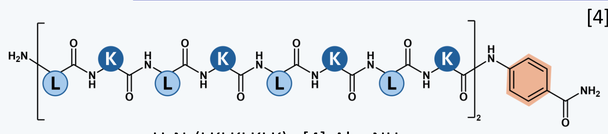




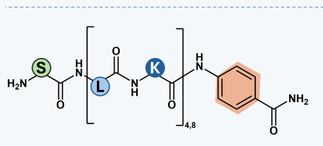
regardless of the specific mixtures, C- and N-terminal modifications of hFF03 lead to the formation of higher ordered structures

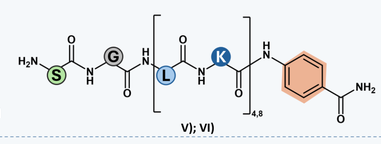
N-terminal glycosylation

[4]

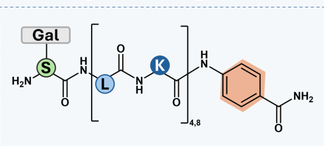


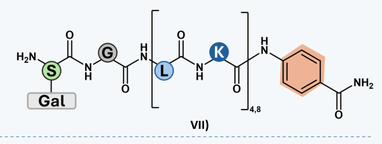
H_2N-(LKLKLKLK)$_2$-[4]-Abz-NH_2



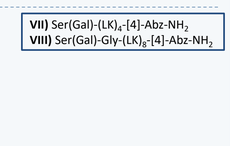


Sequence extension



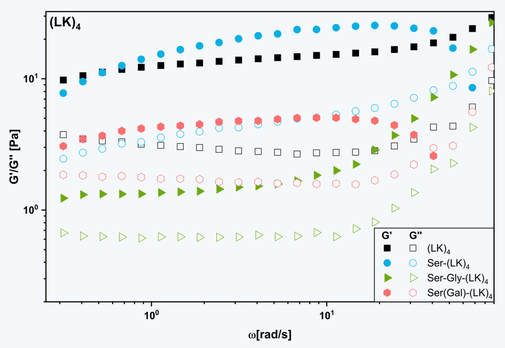


Glycosylation

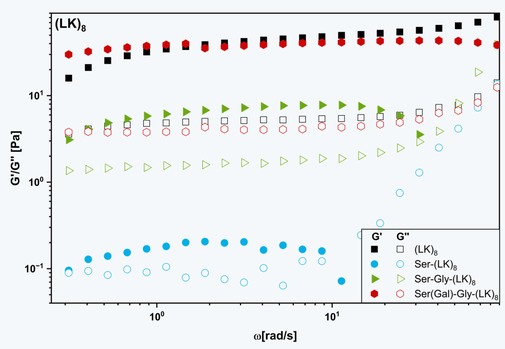


Rheological properties

conditions: c = 0.5 wt%; pH 7.4; 50 mM bis-tris propane + 150 mM NaCl; T = 37° C



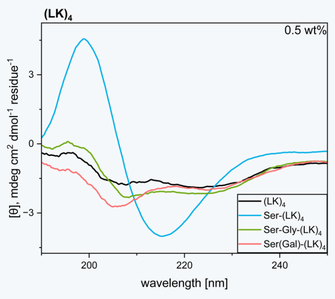
$(LK)_4$ shows minimal change with the addition of one amino acid, while two reduce viscoelastic properties. Glycosylated peptide exhibits stable hydrogel properties.



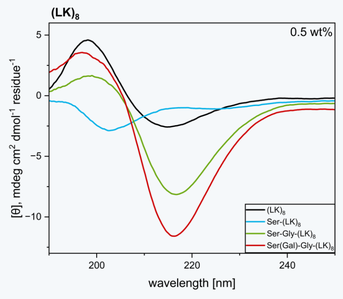
Adding one amino acid drastically reduces $(LK)_8$ viscoelastic properties, while elongation by two forms a stable hydrogel. Glycosylation with a glycine spacer retains viscoelastic properties similar to the unmodified peptide.

Circular dichroism (CD)

conditions: pH 7.4; 50 mM bis-tris propane + 150 mM NaCl; T = 37° C



$Ser-(LK)_4$ adopts beta-structure, whereas the other peptides exihibit likely alpha-helical conformation



Least viscous peptide (Ser-(LK)8) exhibits random coil structure; others adapt beta-sheet confirmation

Outlook

- no-linker glycosylation
- multiple glycosylation
- Glycan in sequence: LK-series
- other cross-linkers

References:

[1] Q. Wang, Y. Zhang, Y. Ma, *Materials Today Bio*, 20 (**2023**), p. 100640; V. Kudryavtseva, M. Otero, J. Zhang, A. Bukatin, D. Gould, G. B. Sukhorukov, *ACS Nanoscience Au*, 3.3 (**2023**), pp. 256–265; T. Tseng, L. Tao, F. Hsieh, Y. Wie, I. Chiu, S. Hsu, *Advanced Materials*, 27.23 (**2015**), pp. 3518–24.
[2] R. García-Sobrino, I. Ruiz-Blas, C. García, H. Reinecke, C. Elvira, J. Radríguez-Hernández, E. Martínez-Campos, A. Gallardo, *Biomaterials Advances*, 159 (**2024**), p. 213826.
[3] A. Puhlmann, C. Baydaroglu, B. Schade, M. Gradzielski, B. Koksch, *Journal of Peptide Science*, 31.11 (**2025**), p. e70059.
[4] S. Chowdhary-Fouquet, R. F. Schmidt, A. K. Sahoo, T. Hohmann, B. Schade, K. Brademann-Jock, A. F. Thünemann, R. R. Netz, M. Gradzielski, B. Koksch, *Nanoscale*, 14(28) (**2022**), p. 10176-10189.

Funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) through the CRC 1449 *Dynamic Hydrogels at Biointerfaces* (ID 431232613). The authors acknowledge the assistance of the core facility BioSupraMol supported by the DFG.



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