Proteoglycan mimics: Synthesis of brush glycopolymers via oxime condensation

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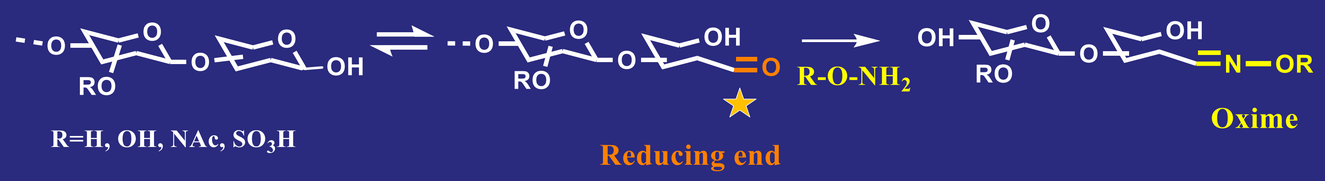
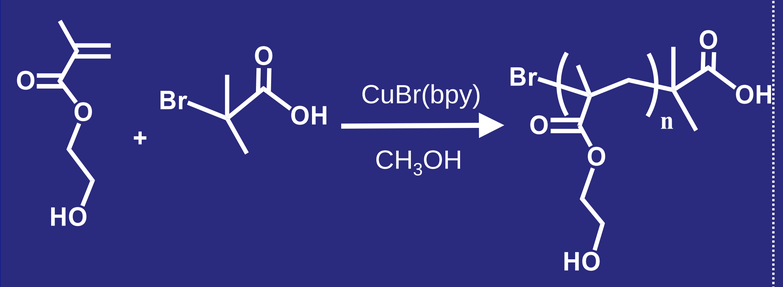
Role of proteoglycans in the extracellular matrix

Proteoglycans (PGs) are key structural and functional macromolecules in the extracellular matrix (ECM). They play an essential role in cell-cell and cell-ECM interactions and thus, determine critical cells processes as adhesion, development, migration, and ultimately cell fate.[1-2] Because of their functions, PGs have been proposed as therapeutics for a variety of diseases.[3] However, the difficulties in PG isolation and purification have hampered their large application and stimulated the development of synthetic mimics.[3] Herein, we describe an approach in which GAGs with long chains (Hyaluronate, HA and Chondroitin sulfate, CS) are attached to poly(2-hydroxyethyl methacrylate) (HEMA) by oxime reaction at the GAG reducing end.

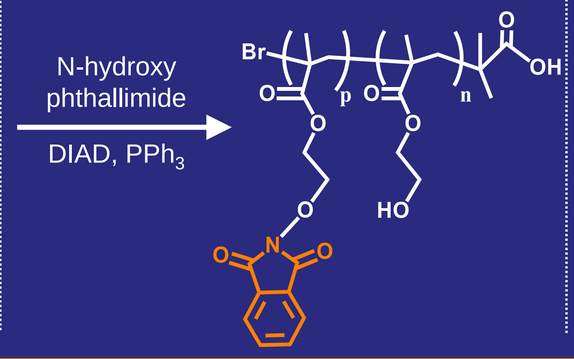
Synthesis of HEMA-GAG copolymers



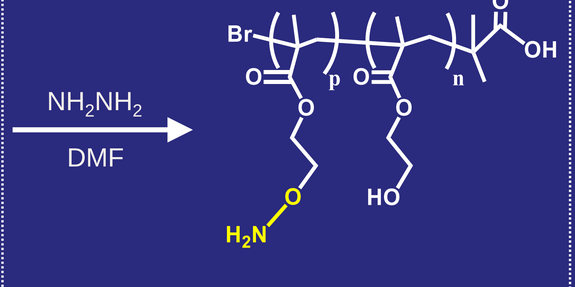
1. Atom transfer radical polymerization



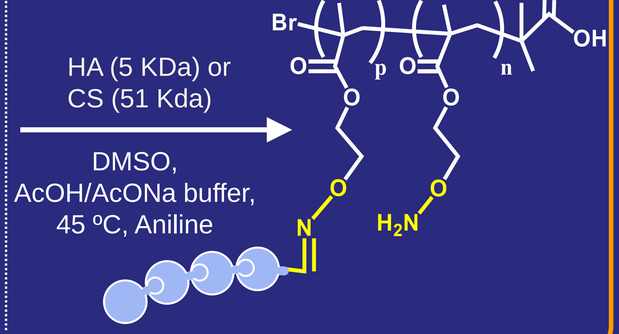
2. Mitsunobu reaction



3. Deprotection

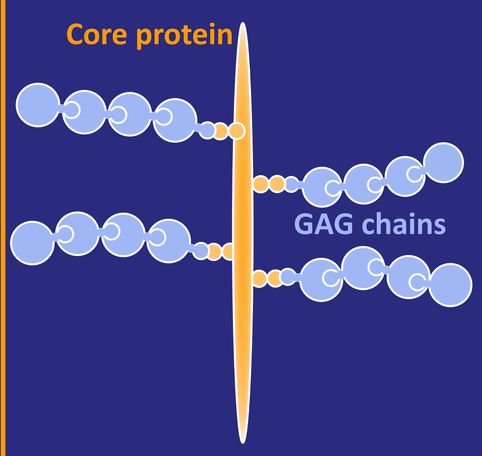


4. Oxime condensation

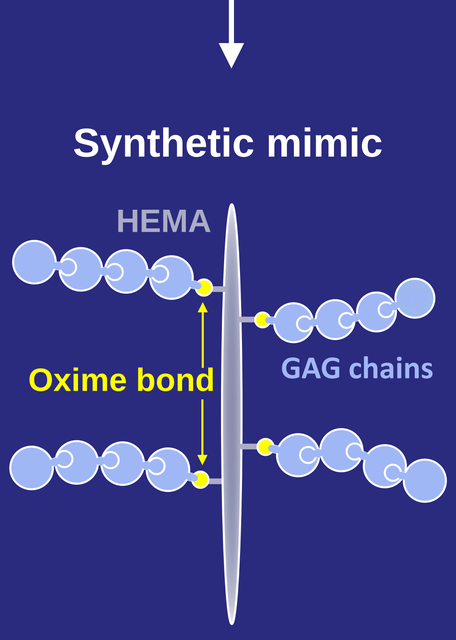


Characterization of GAG-copolymers by NMR and GPC

Native proteoglycan



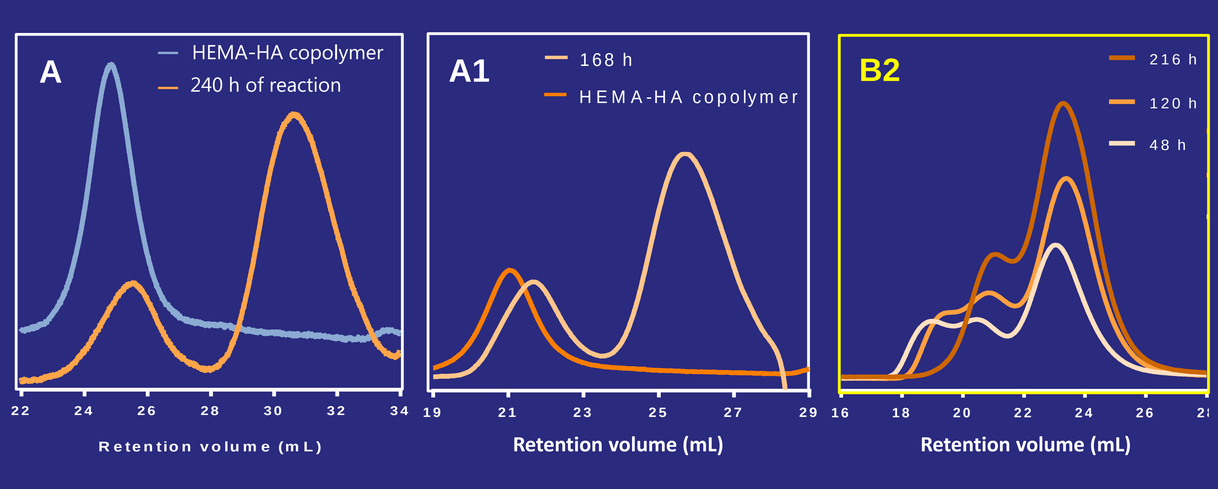
Synthetic mimic



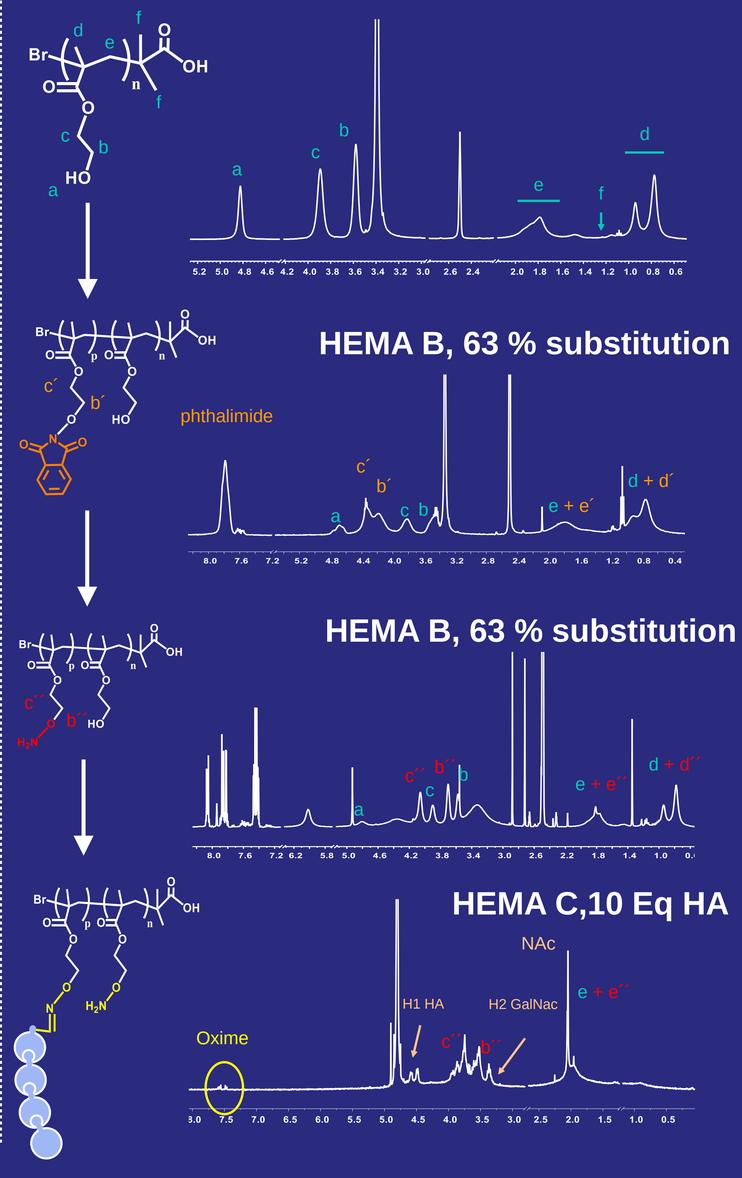
Reaction conditions

	Phthalimide (%)	Eq. GAG	Apparent MW (KDa)	% conversion of GAG to copolymer
A	28	HA 10 (5kDa)	378	22.71
B	63		N.D.	13.85
C	81		327	22.85
D	100		N.D.	29.13
A1	28	HA 20 (5kDa)	537	25.33
B1	63		N.D.	38.80
C1	81		N.D.	14.40
B2	63	CS 10 (51kDa)	N.D.	23.26
B3	63	CS 20 (24kDa)	N.D	9.90
B4	63	CS 20 (60kDa)	N.D	13.90

Gel permeation chromatography (GPC)



^{1}H-NMR spectroscopy



Conclusions

We demonstrate that our synthetic approach is feasible for different GAGs and that the degree of substitution can be tuned: we obtain glycopolymers with different substitution degrees. These outcomes indicate that the generated glycopolymers may be used to develop materials that mimic the extracellular matrix.

References

1. I. Capila and R. J. Linhardt, *Angew. Chem. Int. Ed.*, 2002, **41**, 390
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3. Weyers and R. J. Linhardt, *FEBS Journal*, 2013, **280**, 2511

Acknowledgments

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