Investigating the thermo-responsiveness of poly(*N*-vinylcaprolactam) oligomers and microgels using all-atom molecular dynamics simulations

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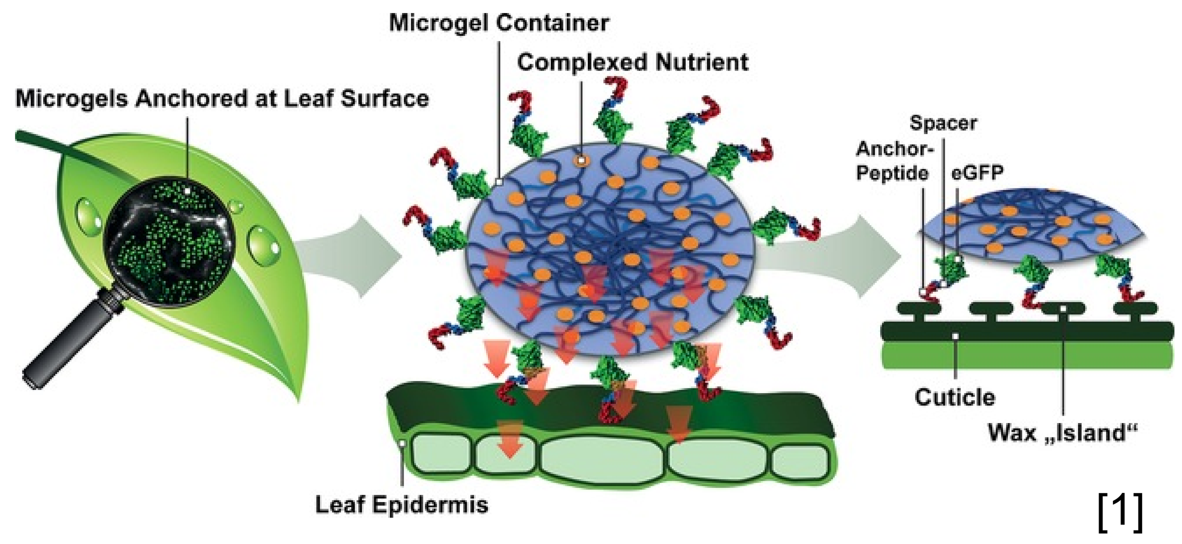
Introduction

Thermo-responsive microgels play a vital role in modern health, life, environment, and plant sciences as they allow a controlled release of substances. Within the BioSC GreenRelease project, microgels "anchored" to crops or weeds are used for a controlled release of herbicides. Initial studies on the general mechanism of ingredient loading and release have been reported [1]. However, knowledge about the detailed processes, at an atomistic level, has remained elusive so far. Using molecular dynamics (MD) simulations, we aim at establishing all-atom models of microgels to investigate loading and release processes.



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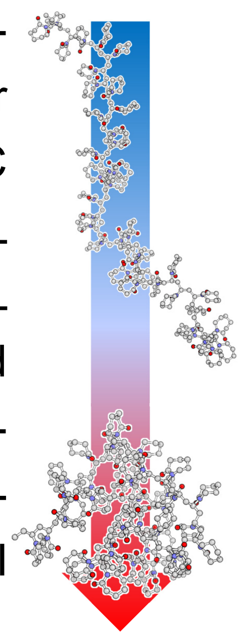
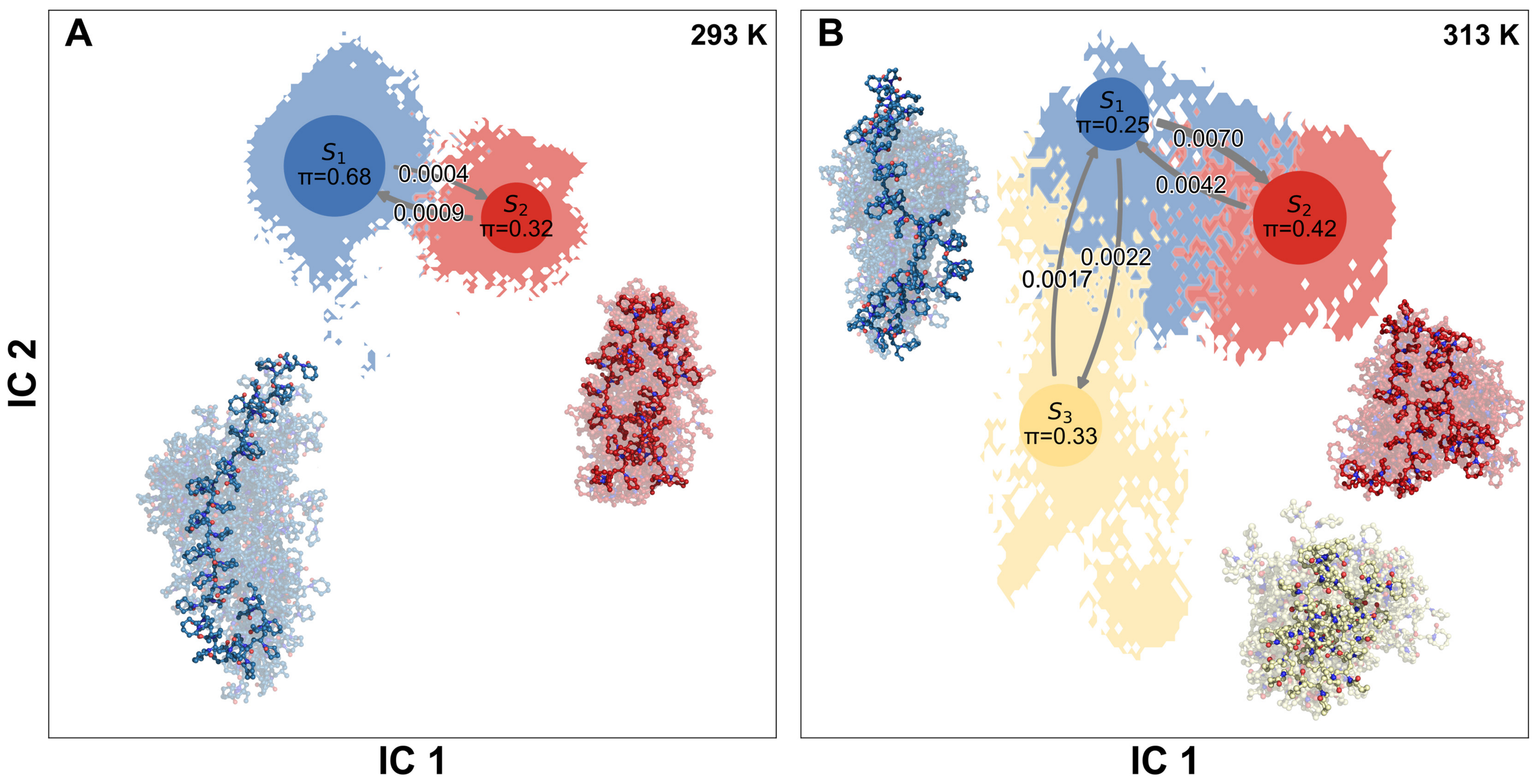
Poly(*N*-vinylcaprolactam) (PNVCL) is a thermo-responsive polymer, which shows a distinct Lower Critical Solution Temperature (LCST) around 35 °C [2]. When exceeding this temperature, the PNVCL polymers become insoluble in water and PNVCL microgels collapse. PNVCL shows ecological and toxicological advantages over other thermo-responsive polymers, such as poly(*N*-isopropylacrylamide) [3], rendering them ideal structures for the use in the greenRelease project.

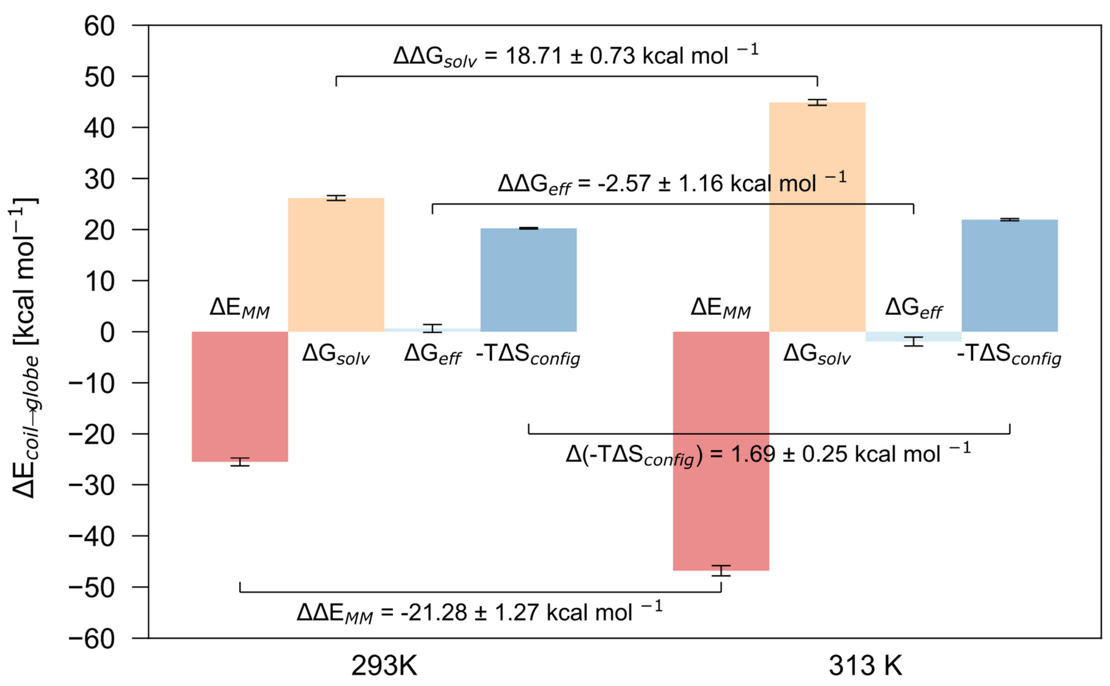


Unraveling the coil-to-globule transition



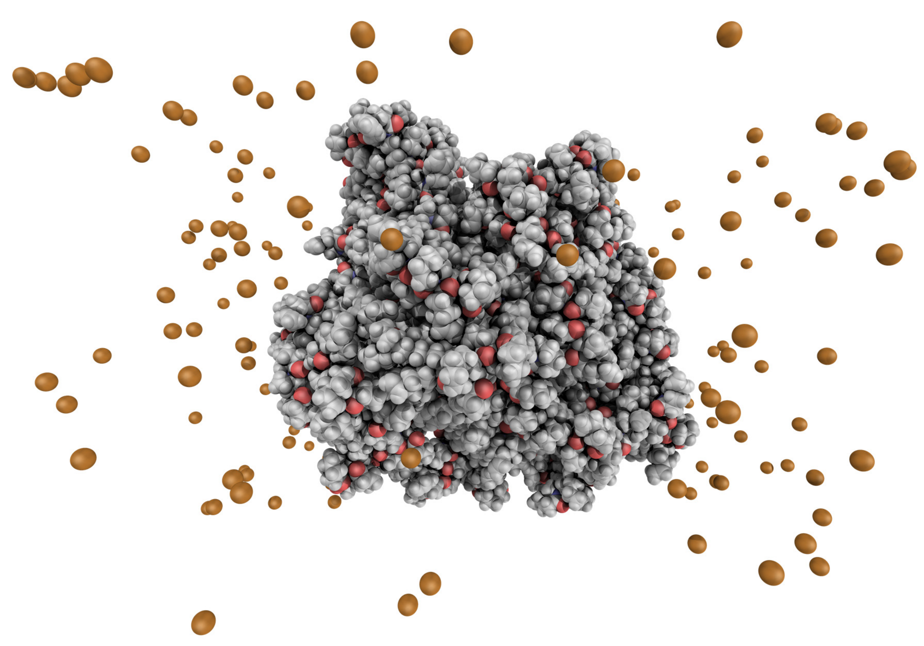
Hidden Markov Models (HMMs) for the coil-to-globule transition of PNVCL reveal a new metastable state and changes in transition rates at elevated temperatures. We constructed HMMs from 10 µs of cumulative simulation time of an atactic PNVCL 40mer below (**A**) and above (**B**) LCST. At lower temperatures, we observe two metastable states, fully extended and hairpin conformation. Going from a semi-collapsed hairpin conformation back to an extended conformation is twice as likely as the folding process at lower temperatures. At higher temperatures the transition rate flips and a more collapsed conformation is favored. Additionally, we identified a new, very compact state at 313 K, which is significantly populated.

MM-PBSA calculations are in agreement with our constructed HMMs. We performed MM-PBSA (Molecular Mechanics Poisson–Boltzmann Surface Area) calculations to further decompose the free energy difference between extended and compact states.



Microgel models & loading processes

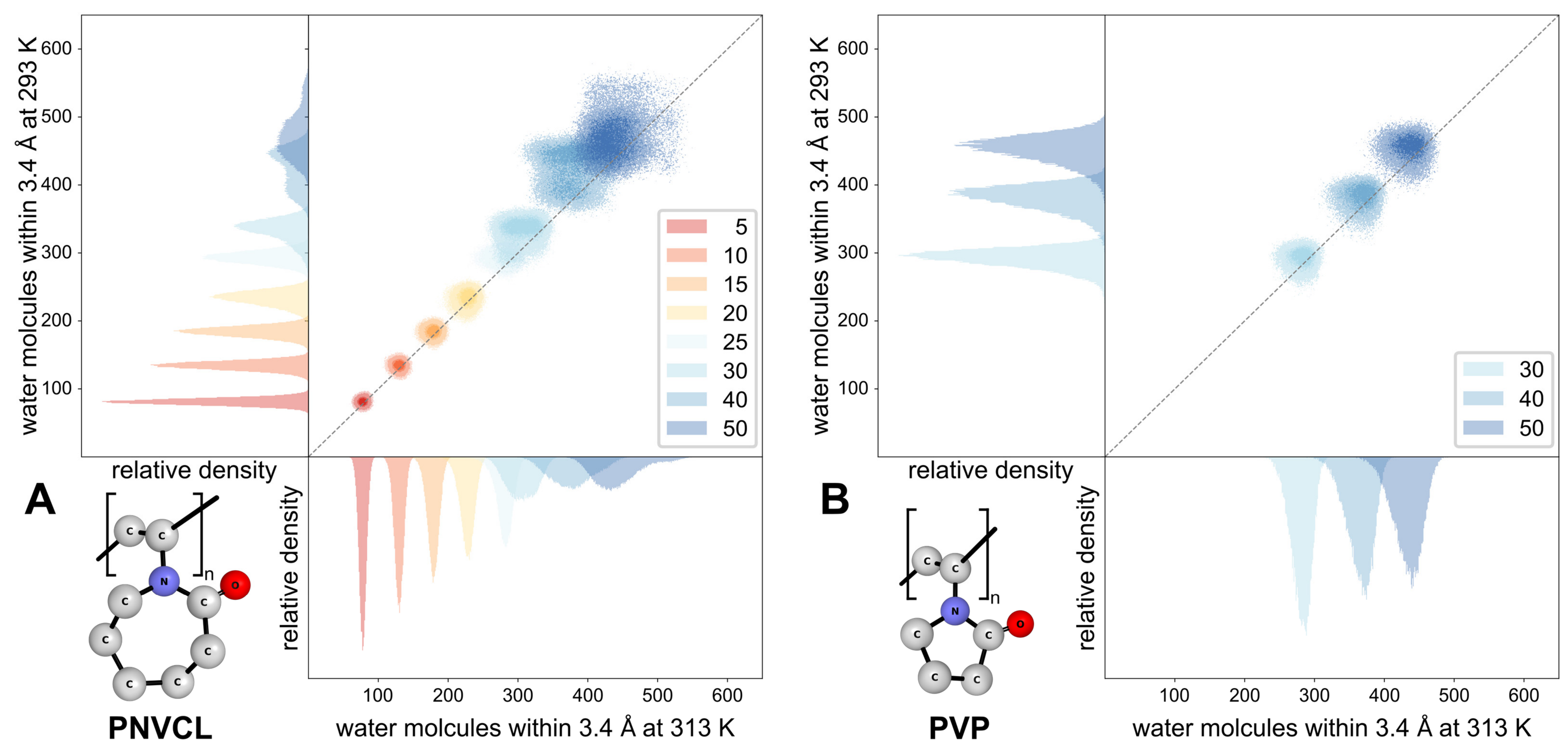
We developed atomistic models of small microgels and investigated the loading of Cu^{2+}. Building blocks of atactic PNVCL 40mers have been modified with additional vinyl groups, which are cross-linked during MD simulations if they meet distance and energy criteria. Obtained models were tested in initial simulations for the microgel's potential to absorb Cu^{2+} ions. Preliminary results are in agreement with our expectations.



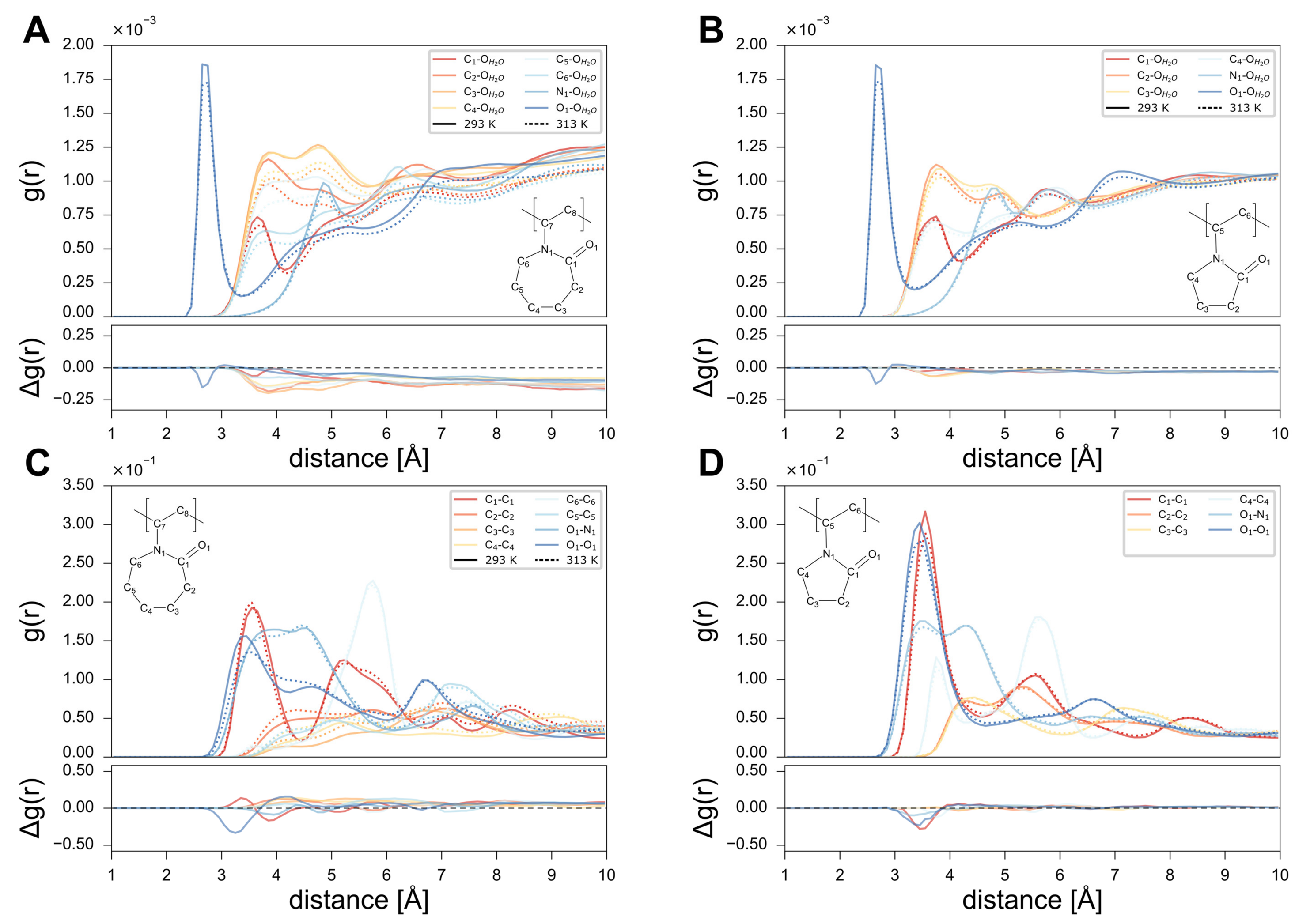
Thermo-responsiveness of PNVCL and PVP

PNVCL is a thermo-responsive polymer, i.e. when a solution of the polymer is heated above the LCST, the polymer becomes insoluble and precipitates. Microgels based on PNVCL similarly show a distinct swelling / collapsing behavior around the same temperature range. Interestingly, poly(*N*-vinylpyrrolidone) (PVP) does not show a thermo-responsiveness, although being structurally similar.

PNVCL shows a distinct loss in solvation at higher temperatures, whereas PVP is barely affected. PNVCL shows a loss in the number of water molecules within the first solvation shell (**A**) at elevated temperatures compared to the solvation at 293 K, whereas PVP is unaffected (**B**).



Why do two additional methylene units matter for the thermo-responsiveness of PNVCL? Radial distribution functions (RDFs) for all atoms of the PNVCL and PVP repeating units and the oxygen atoms of the water surrounding the polymer (**A**,**B**) and to each other (**C**,**D**) show why the two additional methylene units of the PNVCL repeating unit play a major role in the solvation: these show the highest difference in their RDF at different temperatures.



Summary

To investigate the thermo-responsiveness of PNVCL, we simulated PNVCL and PVP oligomers for 585 µs and 75 µs, respectively. We gained insights into the thermodynamics of the coil-to-globe transition by constructing HMMs and performing MM-PBSA calculations. Our simulations yield explanations for the different behavior of PVP, although it being structurally similar to PNVCL. We generated microgel models based on this knowledge and used them in ion loading simulations.

References

1. Meurer, R. A., et al., *Angew. Chem. Int. Ed.* **2017,** *56*, 7380-7386.
2. Cortez-Lemus, N. A., et al., *Prog. Polym. Sci.* **2016,** *53*, 1-51.
3. Vihola, H., et al., *Biomaterials* **2005,** *26*, 3055-3064.

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