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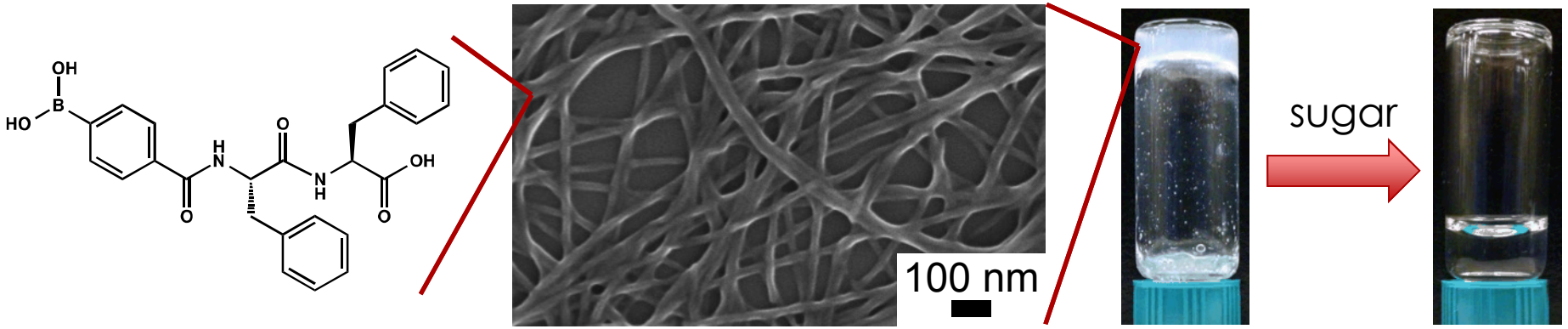

Synthesis and Responsive Self-Assembly of Boronic Acid-Functionalized Peptides

Brad H. Jones, Alina M. Martinez, Jill S. Wheeler,
David R. Wheeler, and Erik D. Spoerke

March 25, 2015

U.S. DEPARTMENT OF ENERGY | NNSA National Nuclear Security Administration

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Microtubules: Dynamic Functional Assemblies

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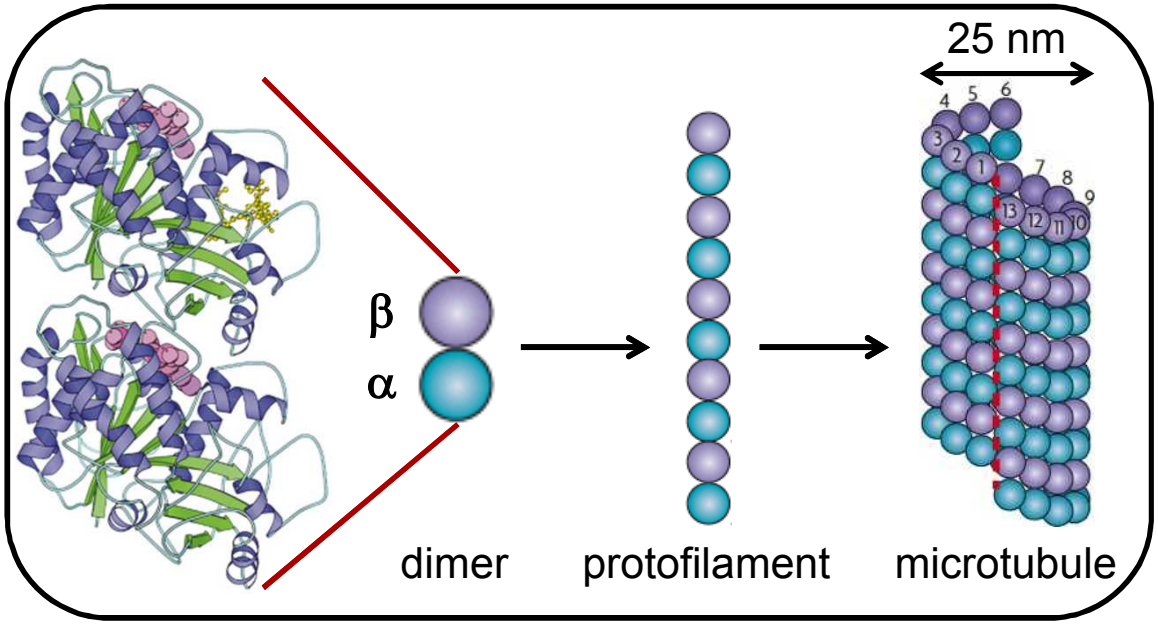
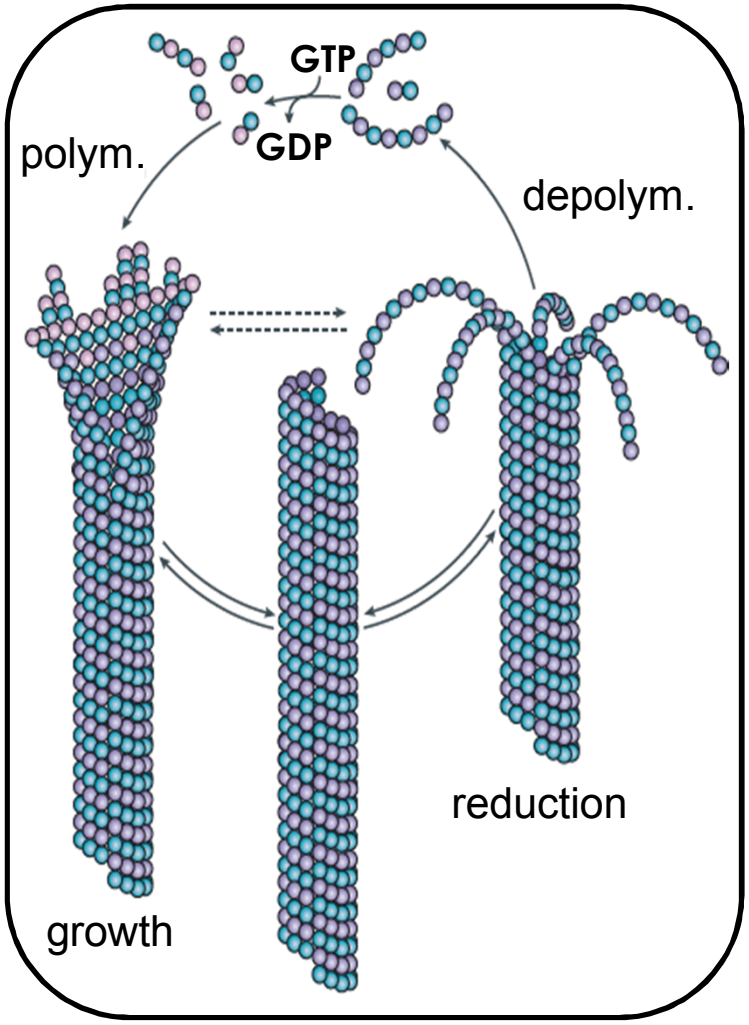
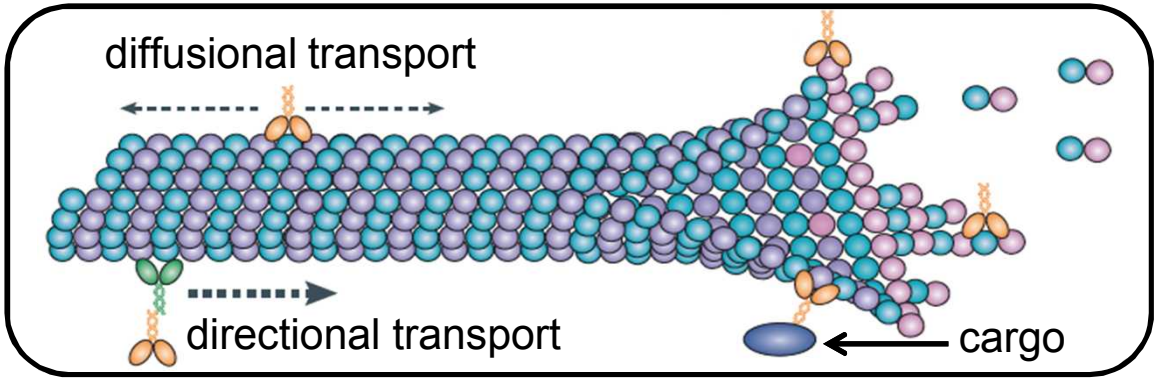
Tubulin microtubules are dynamic, self-assembling entities essential to cell function



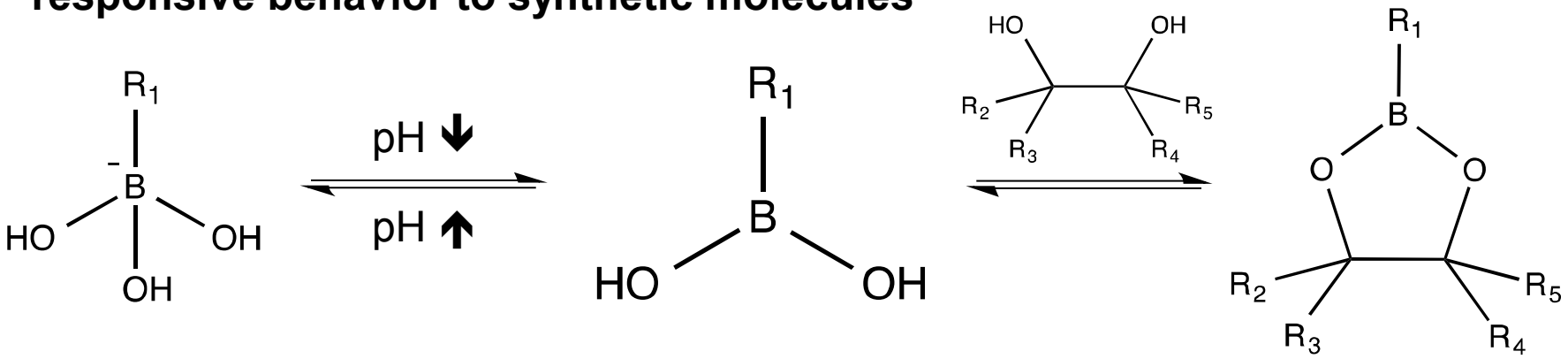


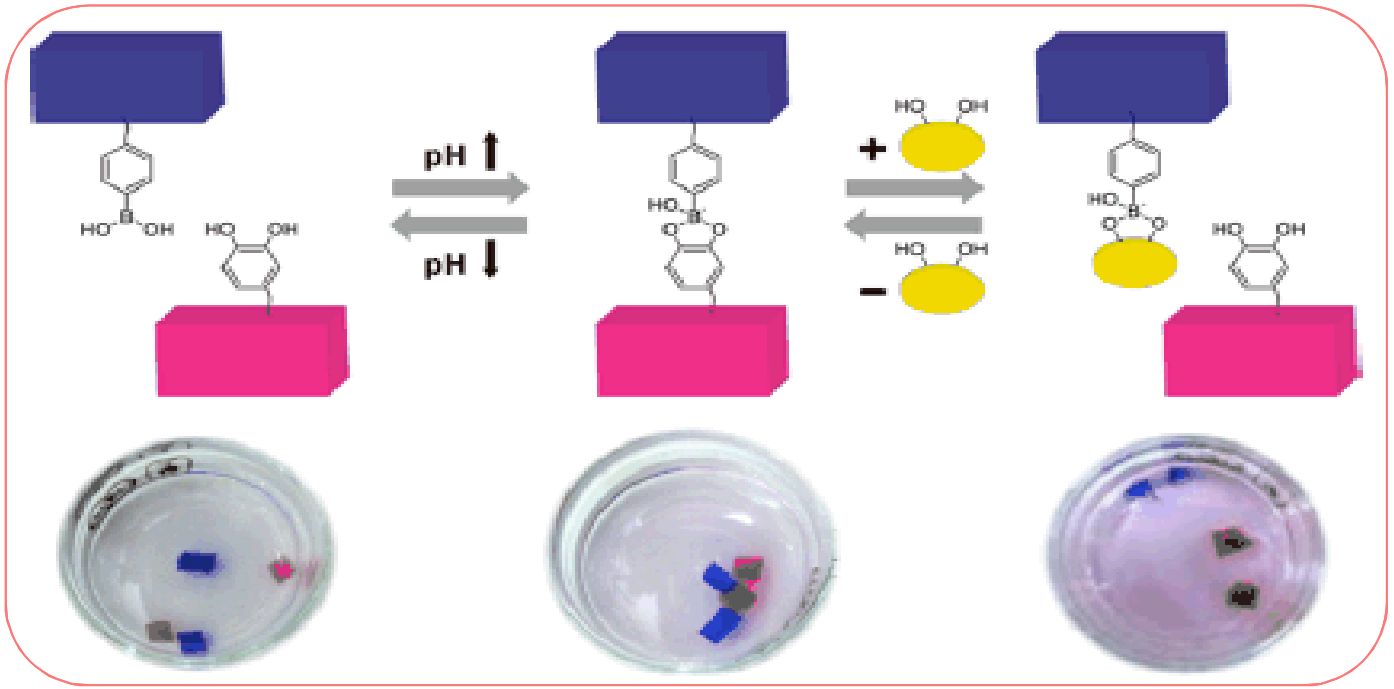


Akhmanova, A.; Steinmetz, M.O. *Nat. Rev. Mol Cell. Bio*. **2008**, *9*, 309-322.
Nogales, E. *Annu. Rev. Biochem*. **2000**, *69*, 277-302.

Boronic Acids

Boronic acids are a convenient chemical functionality to impart responsive behavior to synthetic molecules



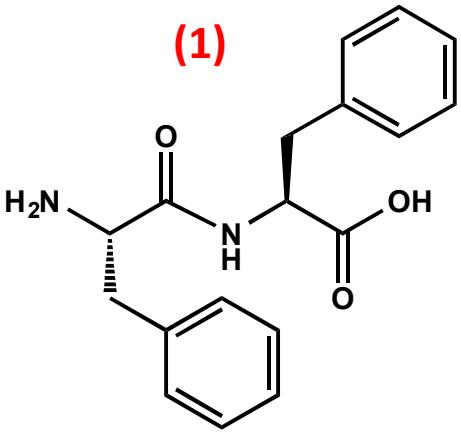


Nakahata, M.; *et al. ACS Macro Lett.* **2014**, *3*, 337-340.

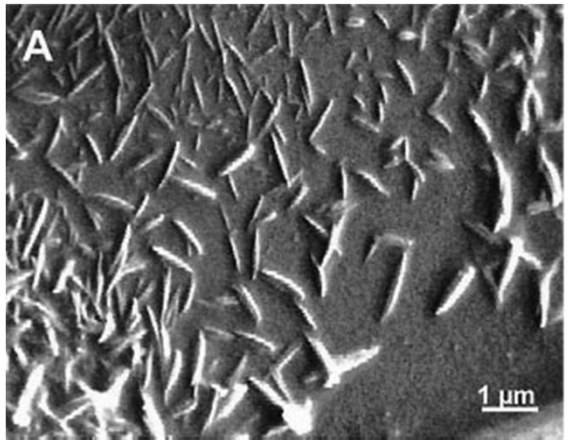
Boronic Acid Peptides

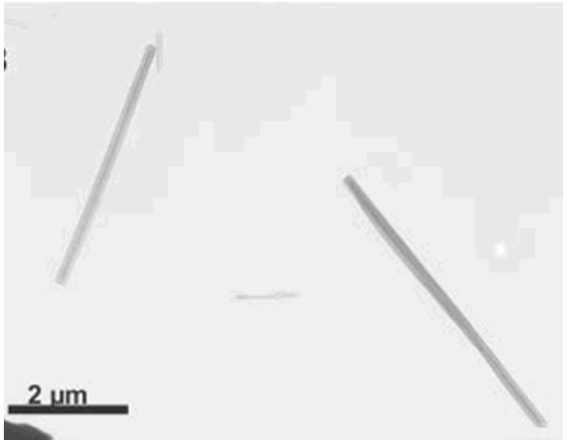
Boronic acid-saccharide interactions have not been well exploited in directing peptide self-assembly

(1)

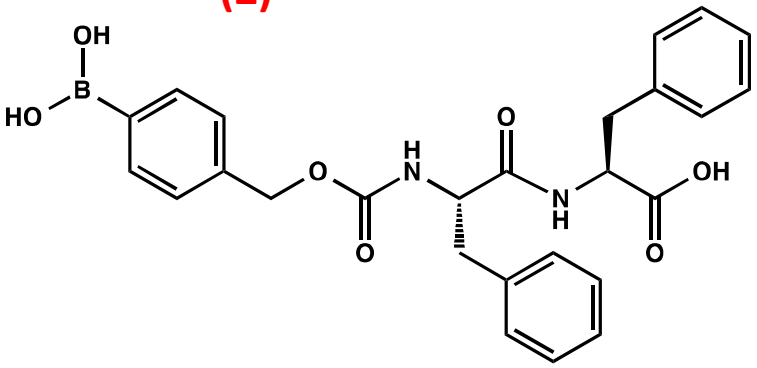


H_2O

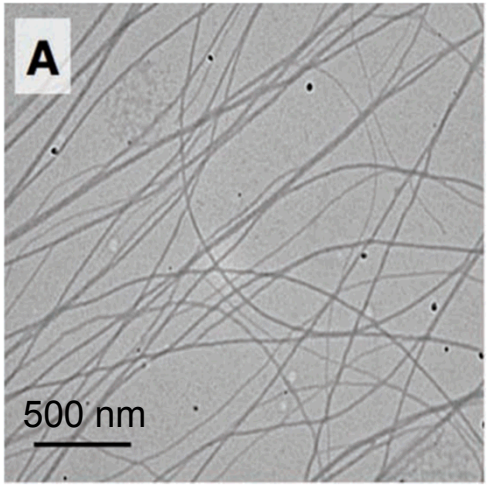


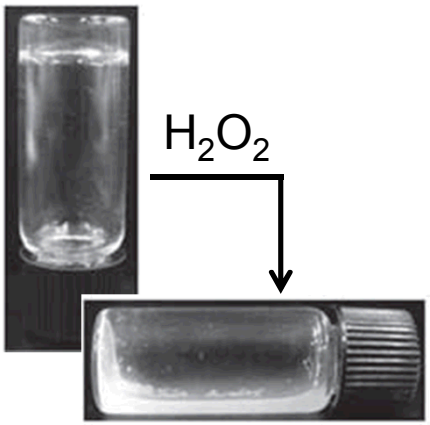


(2)



H_2O



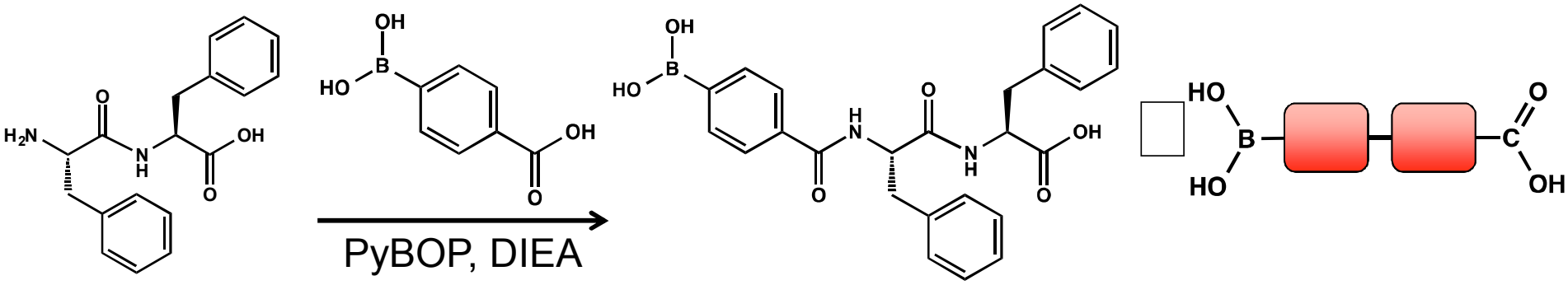


H_2O_2

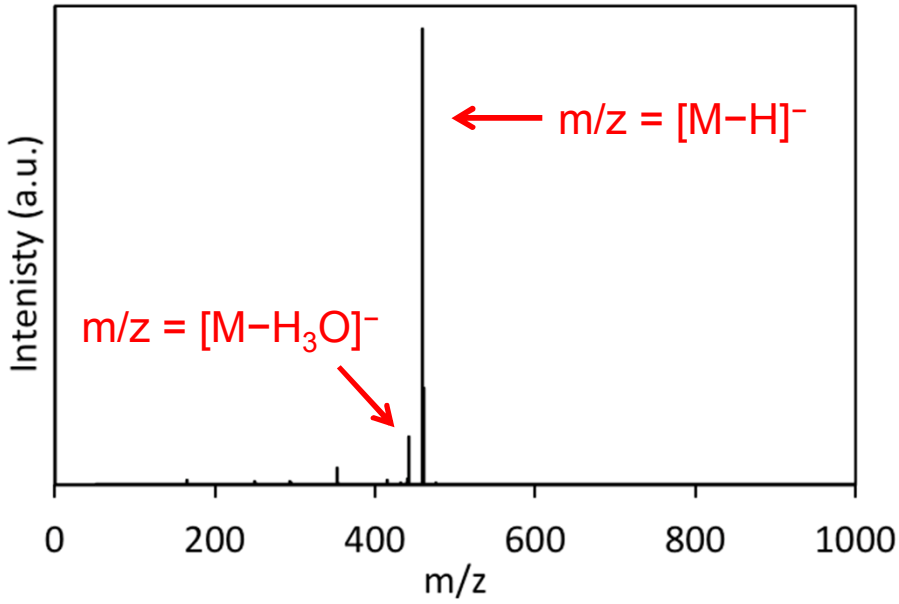
(1) Reches, M.; Gazit, E. *Science* **2003**, *300*, 625-627. **(2)** Ikeda, M.; *et al. Adv. Mater.* **2011**, *23*, 2819-2822.

Boronic Acid Dipeptide Synthesis

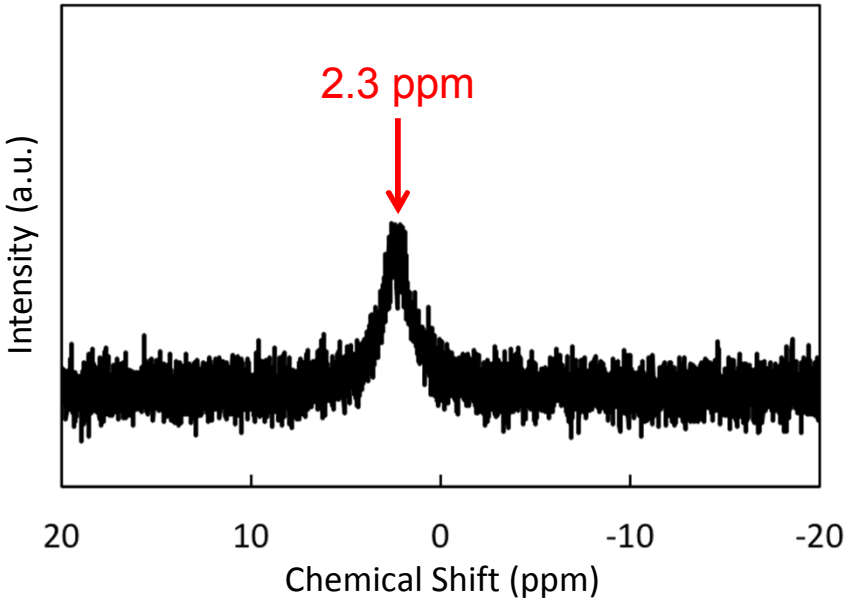
_N_-terminal coupling of carboxyboronic acids is a straightforward route to boronic acid-modified peptides



MS

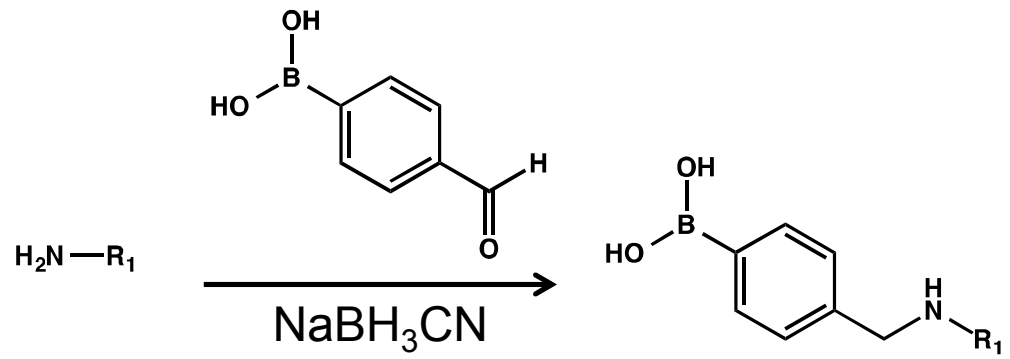


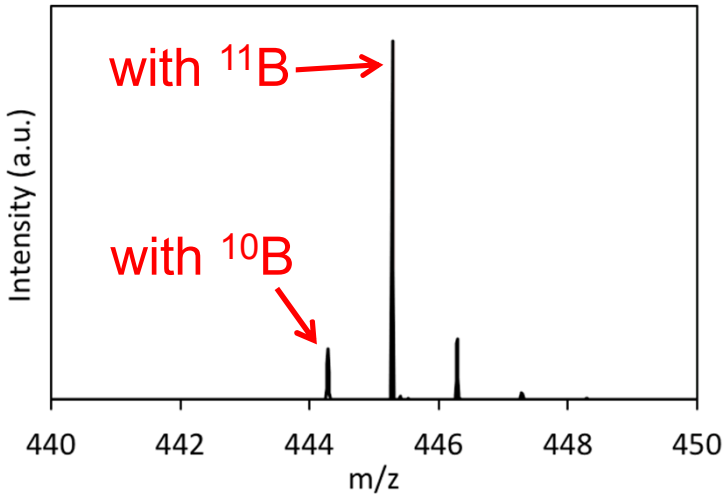
^{11}B NMR

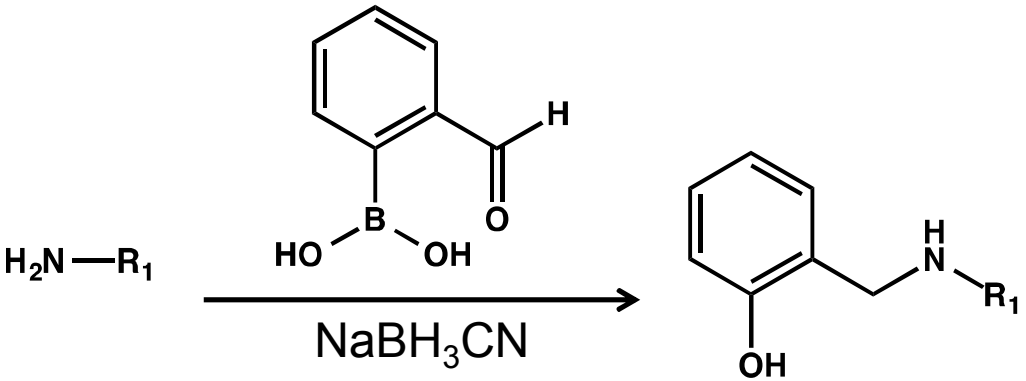


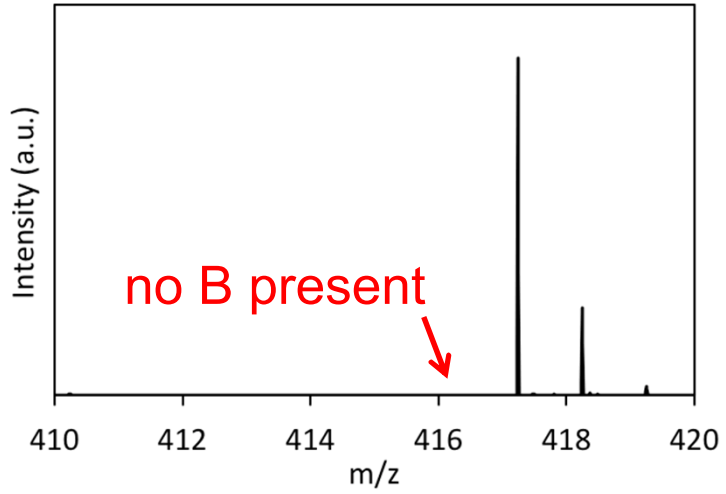
A Caution Regarding Reductive Aminations

Ortho-substituted phenylboronic acids can lead to deboronylated products



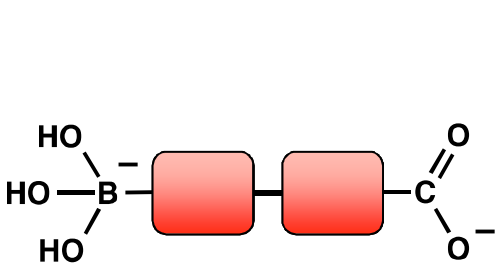






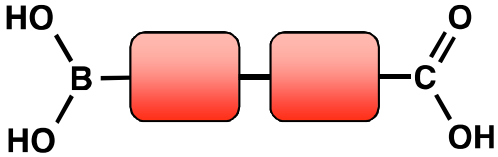
pH-Responsive Self-Assembly

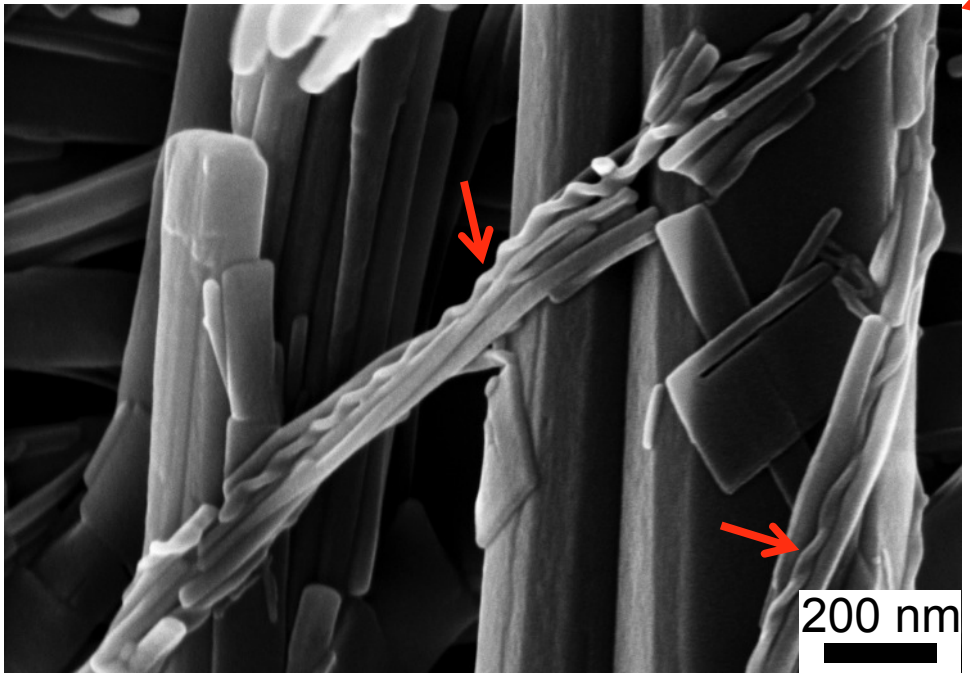
Nanoribbon assemblies are reversibly formed by changes in pH

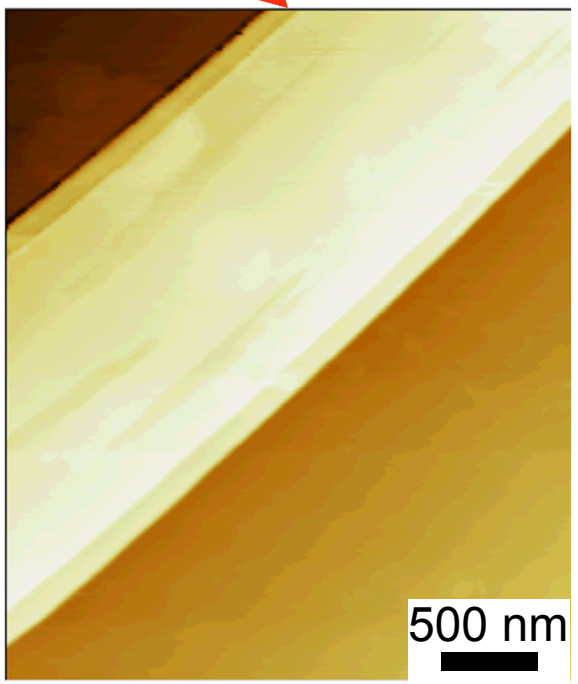


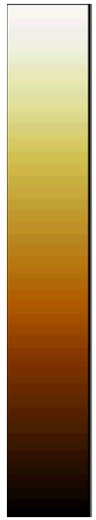
+ HCl, pH ≤ 5

+ NH_4OH, pH ≥ 5









Salt-Responsive Self-Assembly

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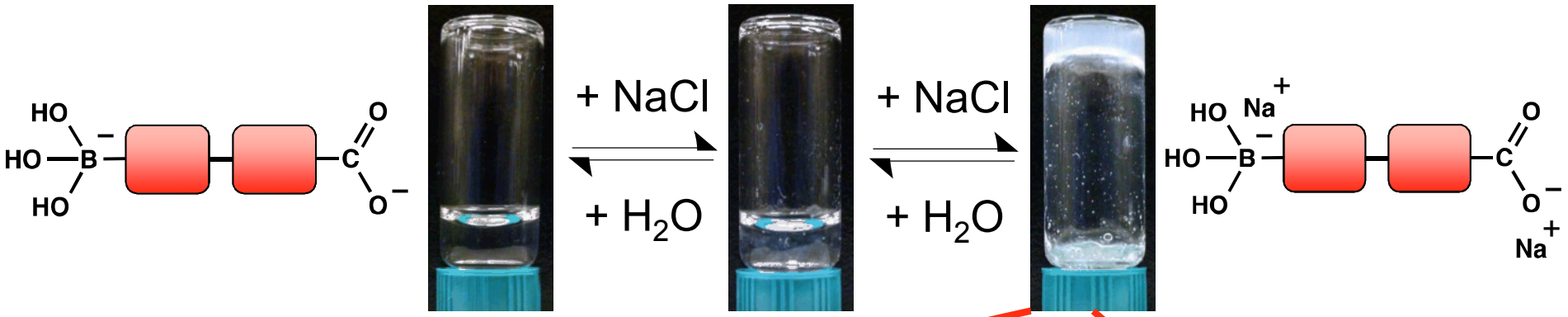
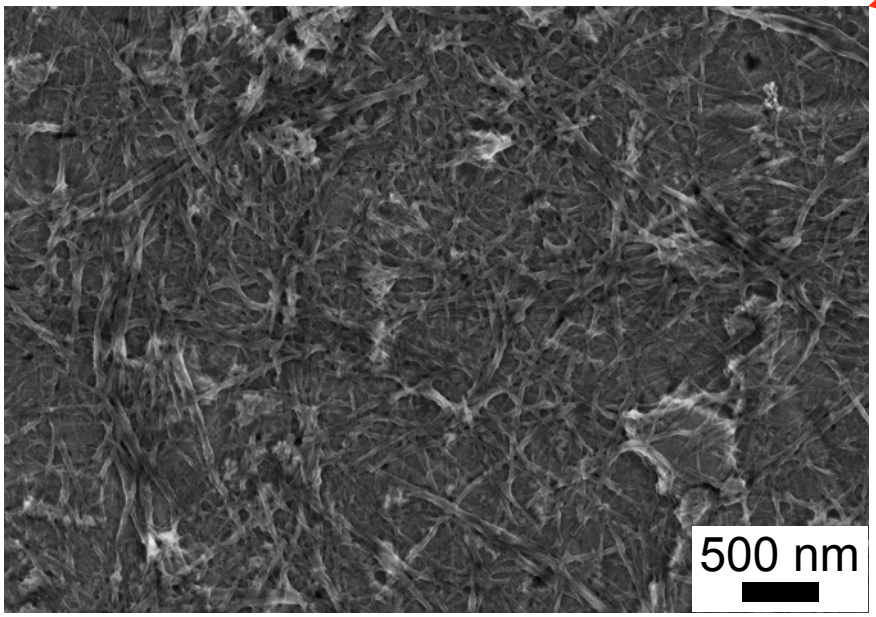
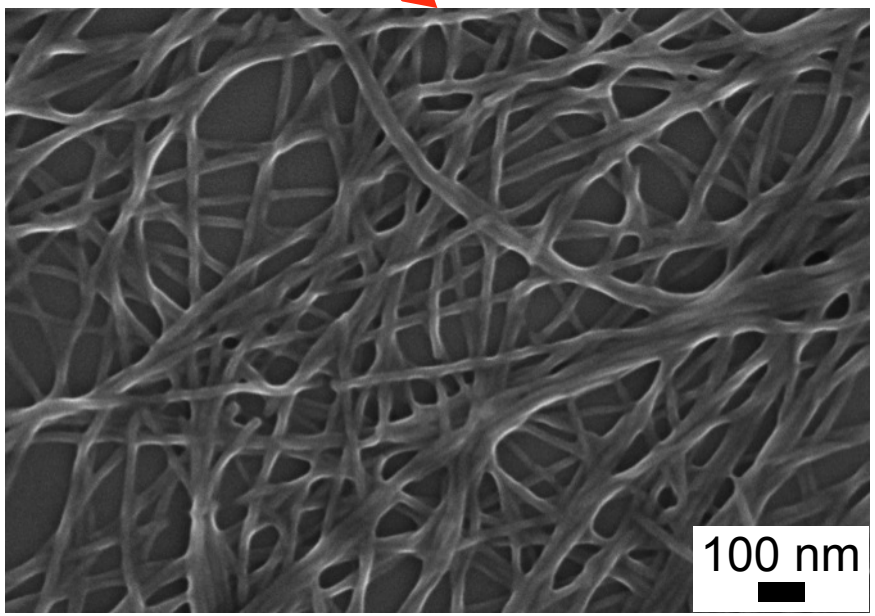
Nanoribbon assemblies are reversibly formed by changes in [salt]

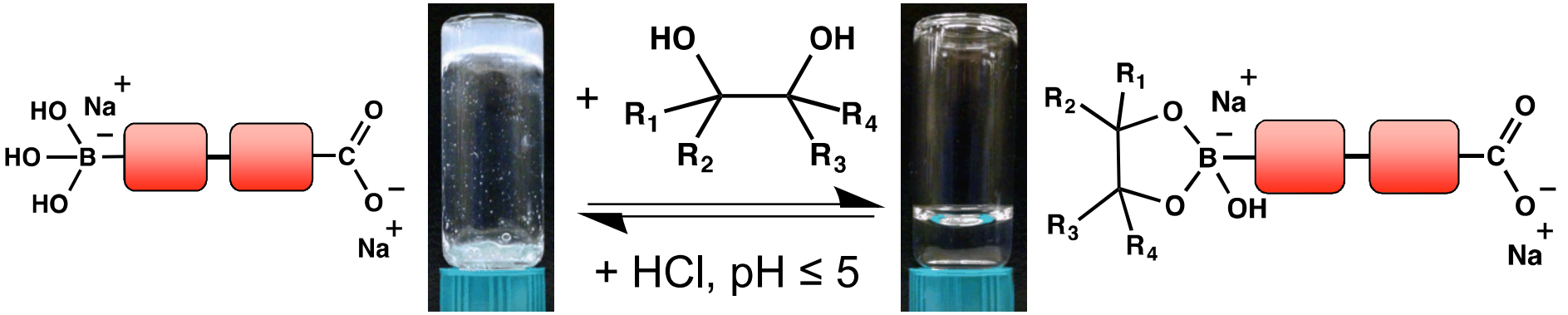


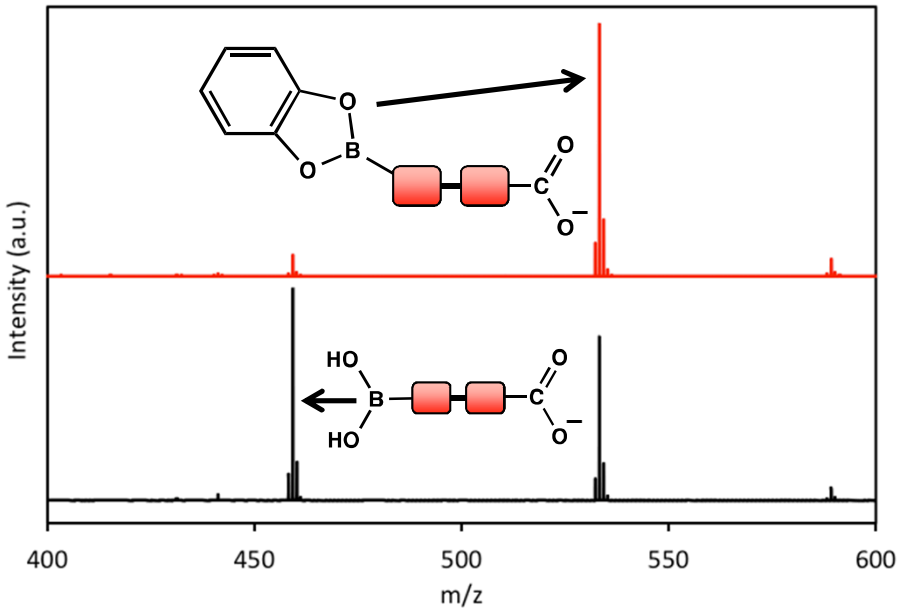




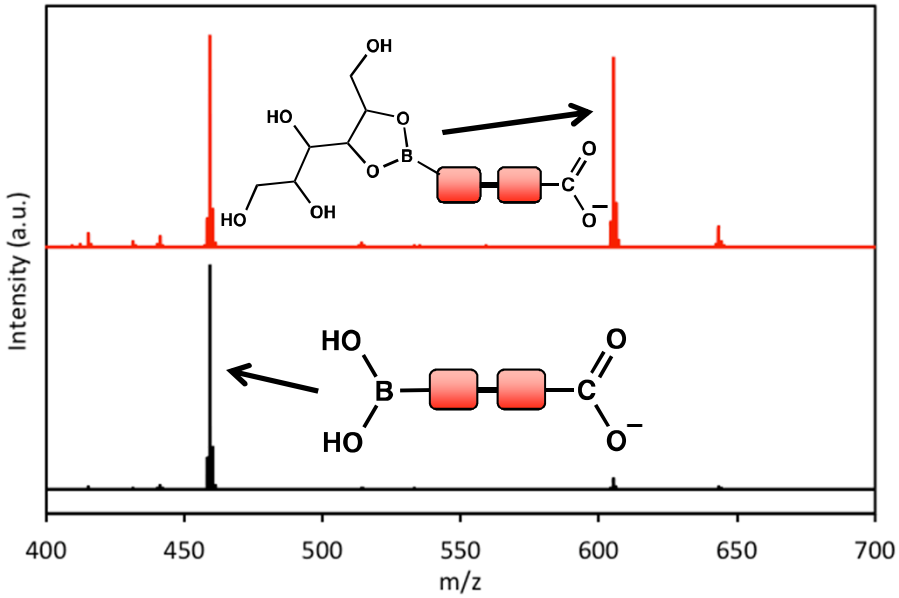
Saccharides/Polyols Induce Disassembly

Gel-sol transitions are triggered by addition of saccharides or polyols





[**catechol**]:[peptide] = 1:1 6:1

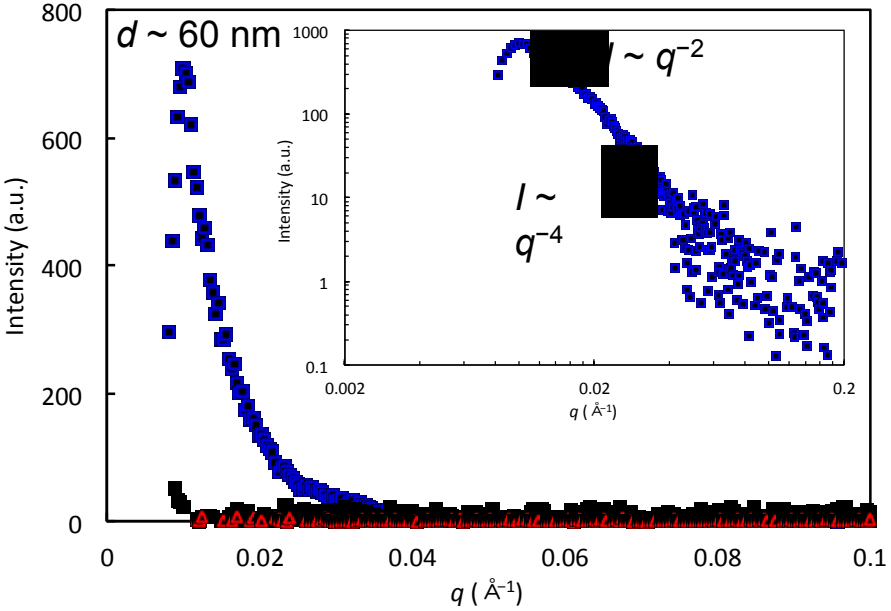


[**sorbitol**]:[peptide] = 1:1 6:1

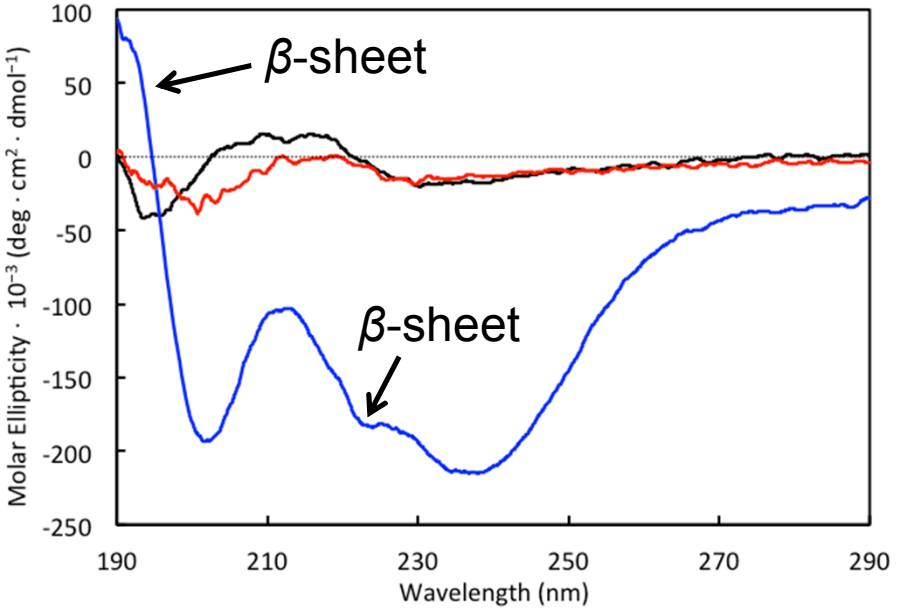
Structural Characterization

Small angle x-ray scattering (SAXS) and circular dichroism (CD) spectroscopy confirm stimulus-induced disorder-order-disorder transitions.

SAXS



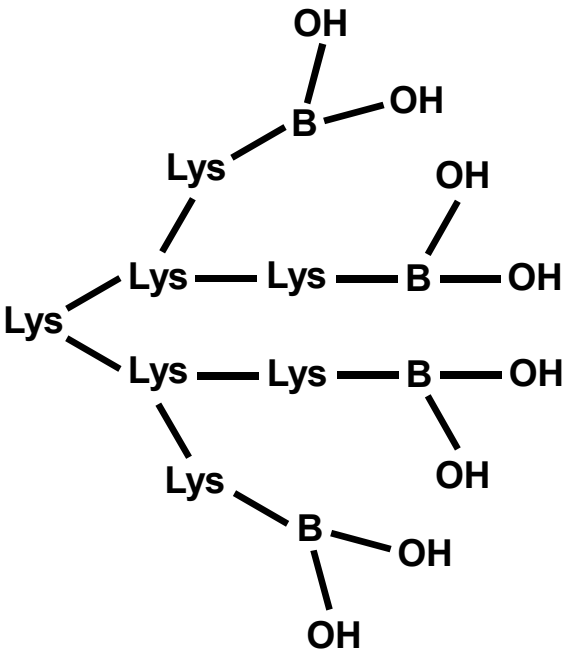
CD

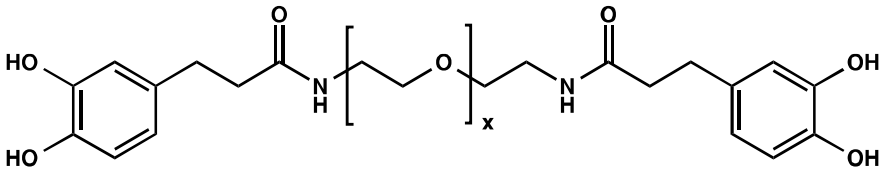


peptide in pH 7 buffer → + NaCl → + catechol

Multi-Functional Peptides

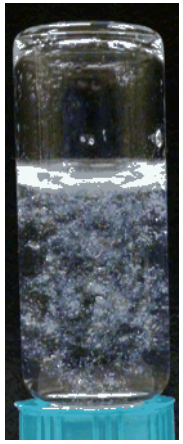
Boronic acid-polyol recognition can also trigger sol-gel transitions in peptides containing multiple boronic acids

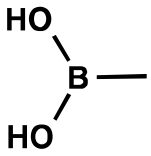




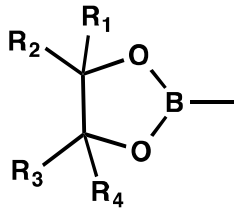
glycoproteins (*e.g.*, avidin)

polysaccharides (*e.g.*, xanthan gum)





pH



Conclusions

- **Boronic acids are synthetically convenient handles for directing the self-assembly of peptides *via* external stimuli**
- **Boronic acid-modified di(phenylalanine) reversibly self-assembles into physically crosslinked nanoribbon networks in response to changes in pH or [salt]**
- **Physical networks can be disassembled by the conversion of boronic acids to boronate esters *via* introduction of polyols/saccharides**
- **The same interactions can be utilized in multi-functional peptides to reversibly introduce chemical crosslinks**

Acknowledgements

- **Lance Miller and Dr. James Hochrein** – mass spectrometry
- **Bonnie McKenzie** – scanning electron microscopy
- **This research was supported by the U.S. Department of Energy, Office of Basic Energy Sciences, Division of Materials Sciences and Engineering, Project KC0203010**