



Alexander D. Claiborne, Megan S. Rothenberg, Zachary L. Zimmerman, Sirilak Mekcham, Owen A. Lee, Megan R. Hill

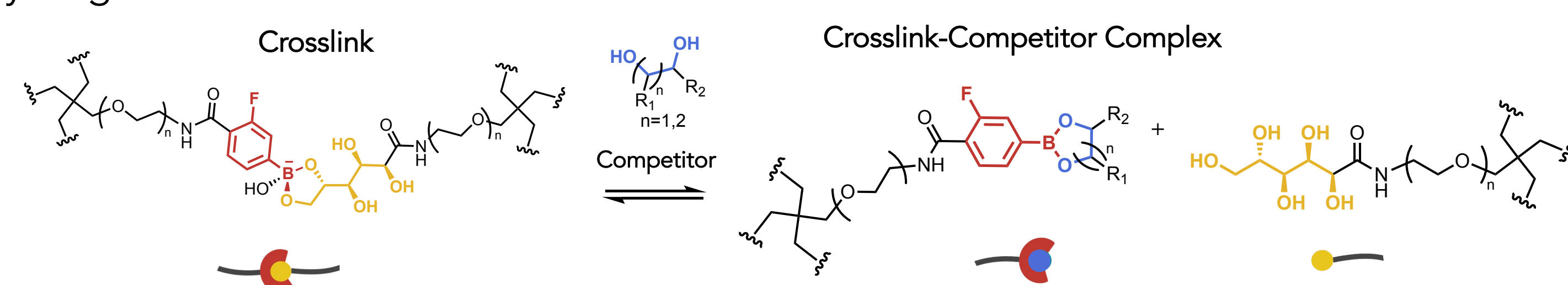
Introduction to Chemistry of Dynamic Hydrogels

Hydrogels with reversible crosslinks have desirable material properties like viscoelasticity, and stiffness similar tissues in the body. These properties are determined by the chemical properties of the crosslink.

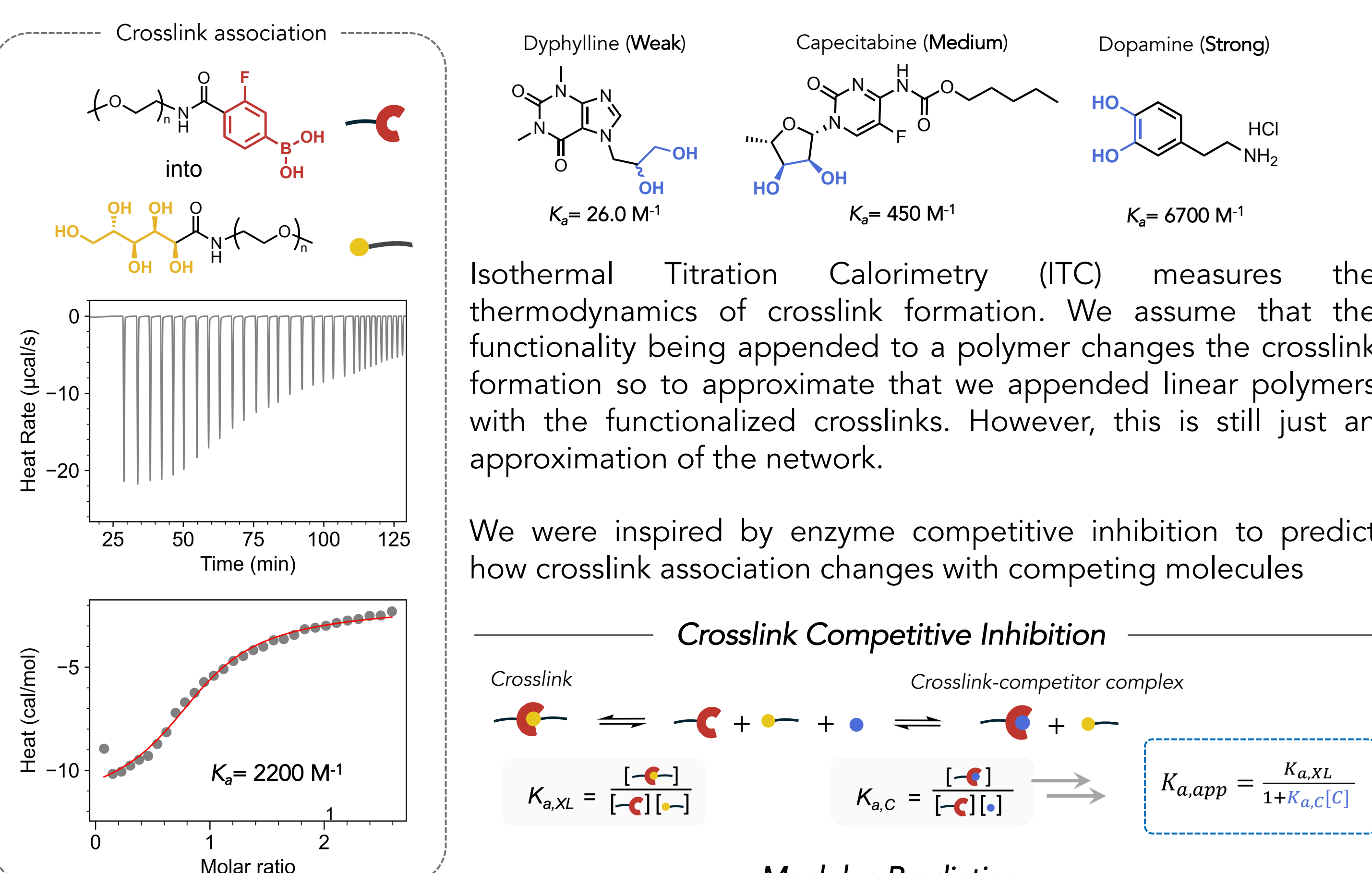


Competitive Inhibition of Dynamically Crosslinked Hydrogels

Purpose: To determine how small-molecule competitors alter crosslink association and hydrogel mechanics.

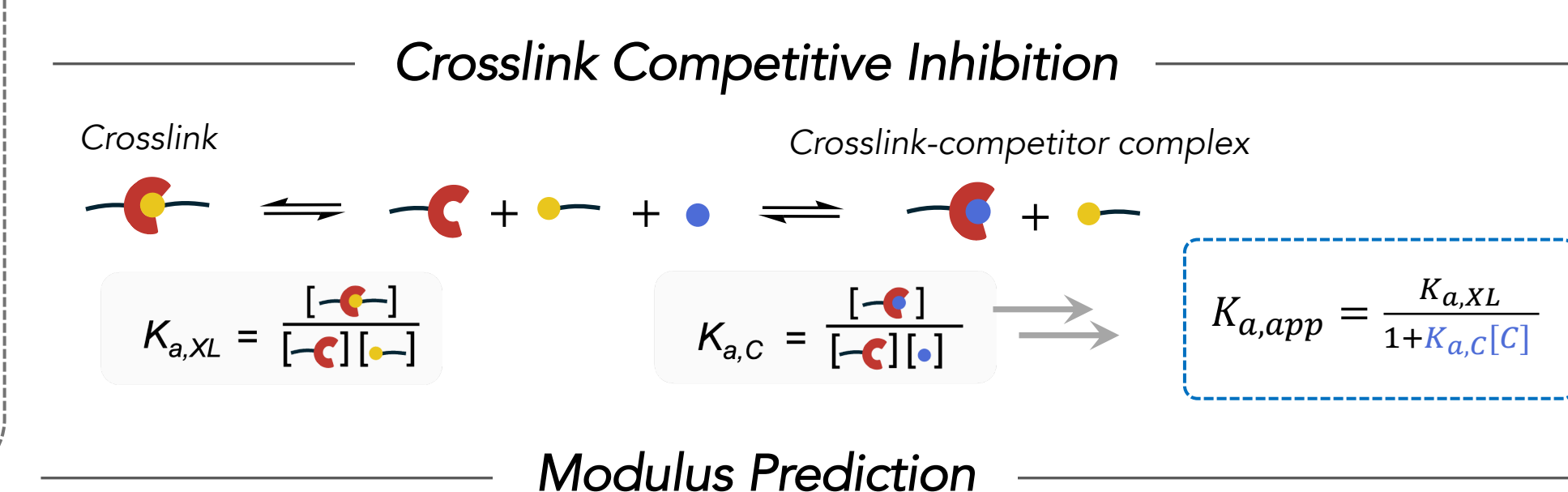


Measuring and Modeling Crosslink-Competitor Association



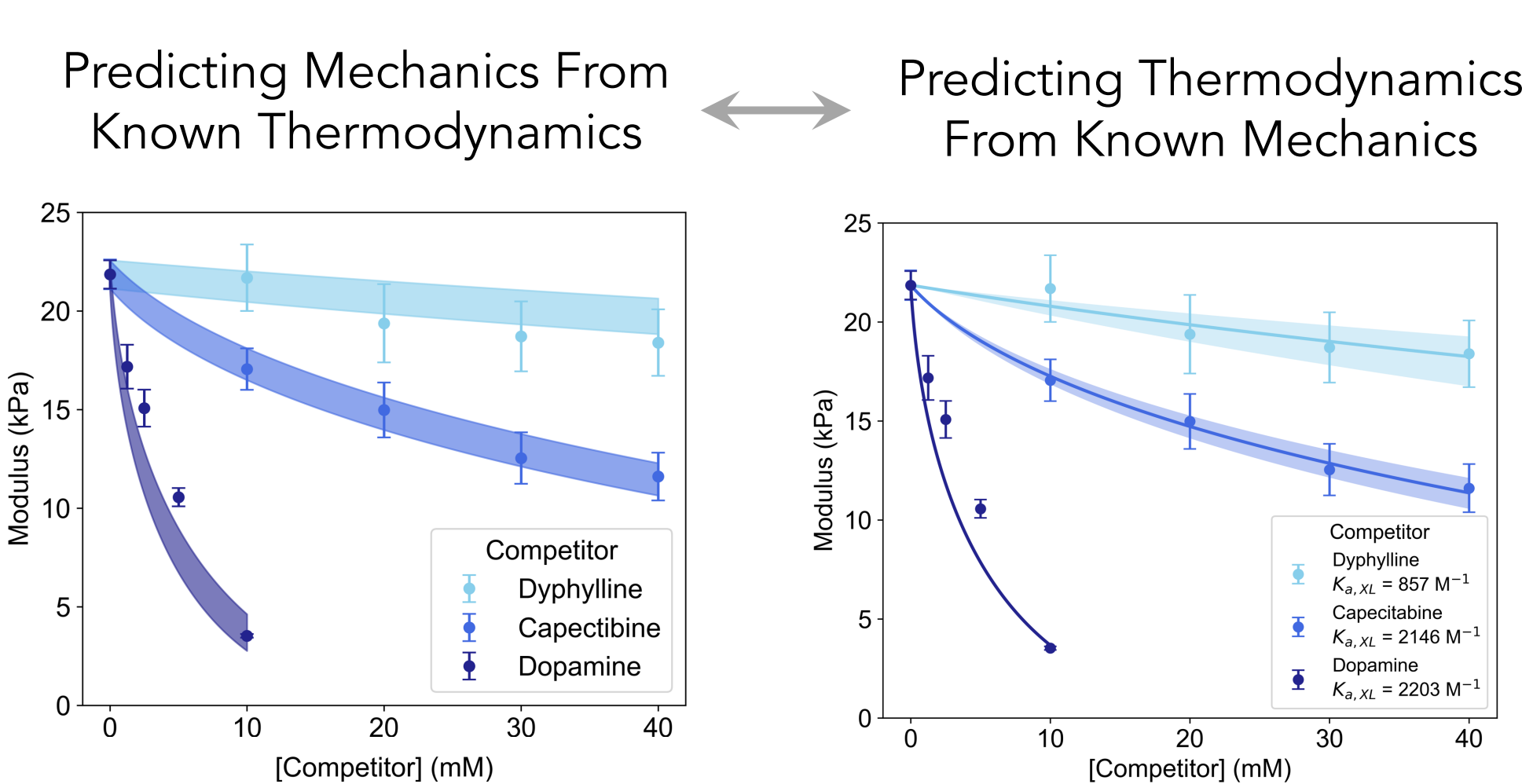
Isothermal Titration Calorimetry (ITC) measures the thermodynamics of crosslink formation. We assume that the functionality being appended to a polymer changes the crosslink formation so to approximate that we appended linear polymers with the functionalized crosslinks. However, this is still just an approximation of the network.

We were inspired by enzyme competitive inhibition to predict how crosslink association changes with competing molecules



$$p = \left(1 + \frac{1}{2N_{XL}K_{a,app}}\right) - \left[\left(1 + \frac{1}{2N_{XL}K_{a,app}}\right)^2 - 1\right]^{1/2} \rightarrow G_p/k_B T = \frac{N_{XL}}{16} \left(3 - \sqrt{\frac{4}{p} - 3}\right)^3 \left(\sqrt{\frac{4}{p} - 3} + 1\right)$$

Applying Model to Observed Mechanical Changes



Claiborne, A. D.; Mekcham S.; Lee, O., A.; Hill, M., R.; ACS Cent. Sci. 2026, 12 (2), 233-242.

Key Result
Competitor alters mechanics predictably, mechanical changes can predict polymer binding affinity.

Want to see how competitive inhibition can be used in your gels?? Check out our web-app!

inhibnet.streamlit.app

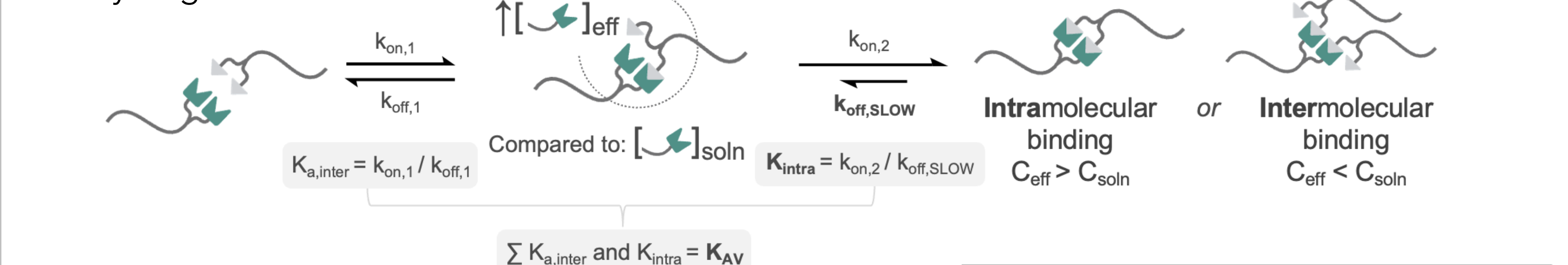


Reversible chemical interactions govern many useful polymer properties but can be difficult to measure directly. Across three case studies, we pair bulk measurements with molecular models to reveal how these interactions control material behavior.

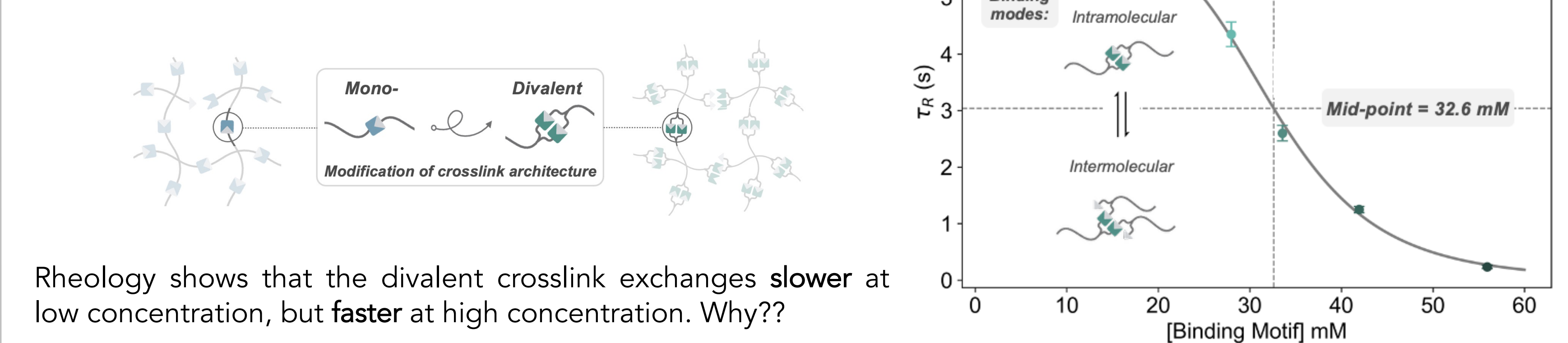
- (1) **Competitive hydrogels:** Competitive inhibition predictably shifts hydrogel mechanics, allowing rheology to quantify crosslink association.
- (2) **Multivalent hydrogels:** Relaxation switches with polymer concentration, consistent with the effective concentration of multivalent binding groups.
- (3) **Polymer frustrated Lewis pairs:** Polymer-supported Lewis pairs catalyze more efficiently than small-molecule analogues.

Multivalent Hydrogels

Purpose: To determine how clustering binding groups at polymer chain ends alters crosslink binding and hydrogel mechanics.



Experimentally Observing Multivalent Behavior

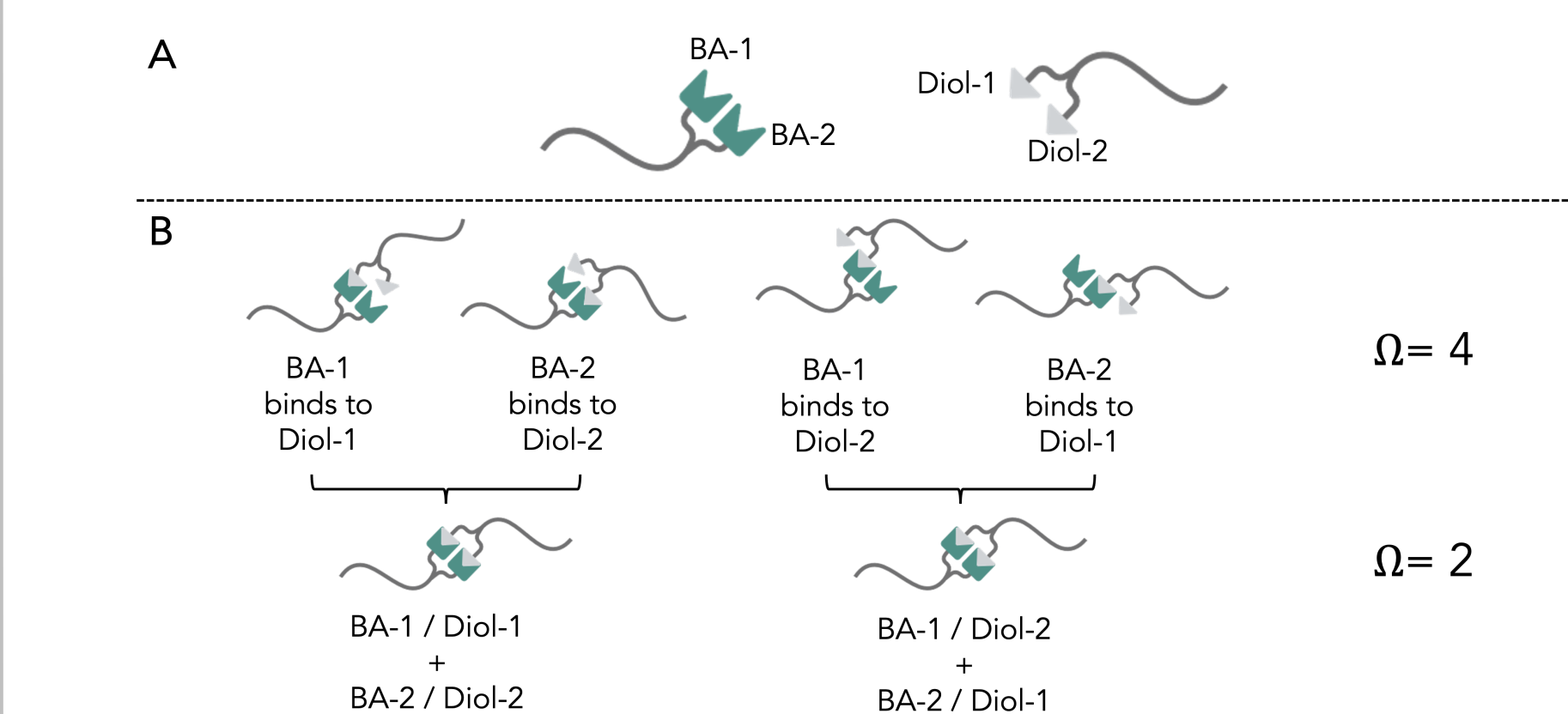


Quantifying the Effective Concentration Gain of a Divalent Crosslink

Degeneracy and Binding Constants Approach

Degeneracy (Ω_i) describes the number of distinct ways i ligand-receptor pairs can form. For this divalent system, $\Omega_1=4$ and $\Omega_2=2$.

$$\Omega_i = \binom{n_{diol}}{i} \binom{n_{ba}}{i} i! = \frac{n_{diol}! n_{ba}!}{(n_{diol}-i)! (n_{ba}-i)! i!}$$



Weighting each binding state by its degeneracy gives the apparent avidity:

$$K_A^{AV} = \Omega_1 K_{A,inter} + \Omega_2 K_{A,inter} K_{intra} + \Omega_3 K_{A,inter} K_{intra}^2 + \dots$$

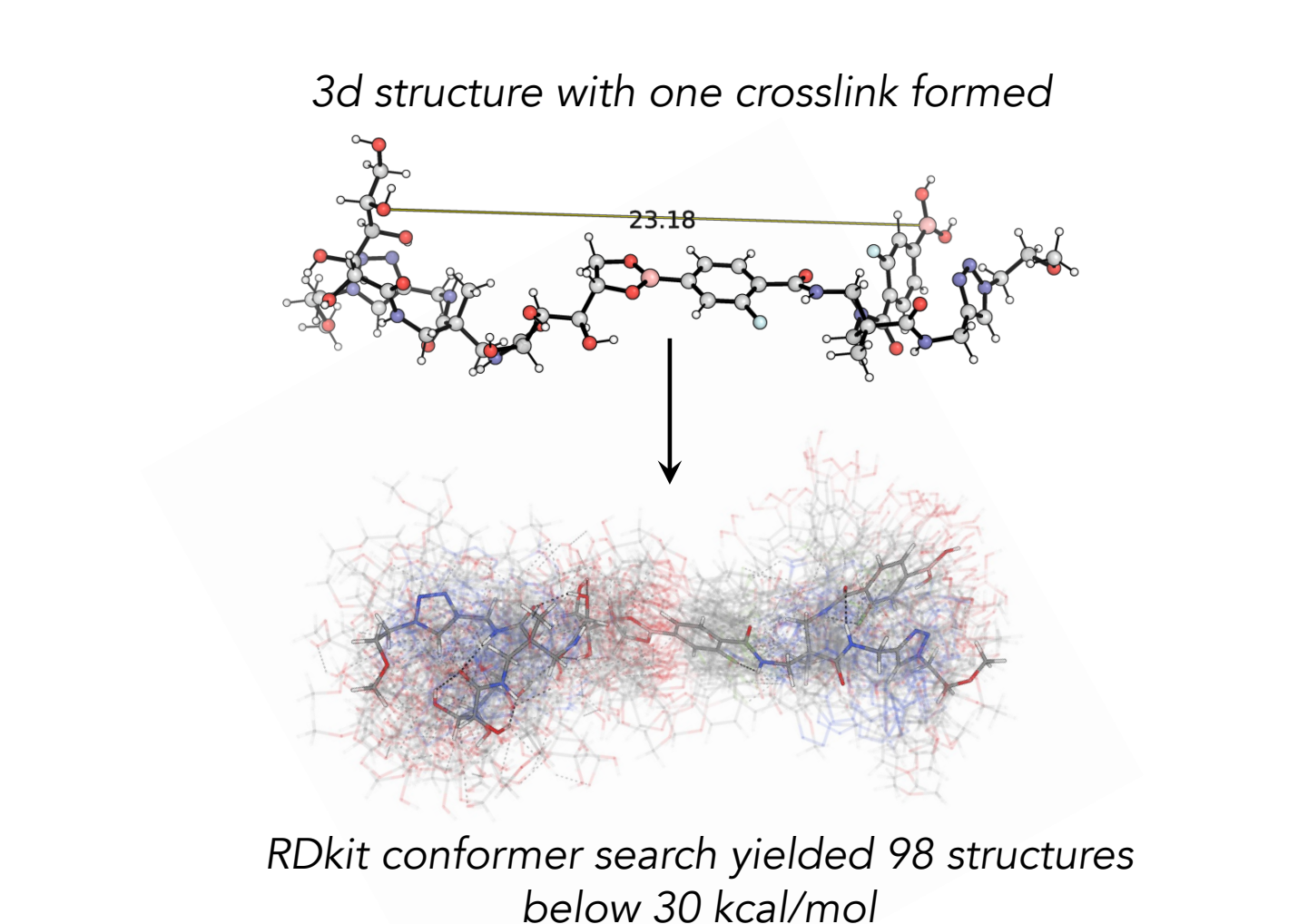
$$K_A^{AV} = 4K_{A,inter} + 2K_{A,inter} K_{intra}$$

ITC measurements of K_A^{AV} and $K_{A,inter}$ were used to calculate $K_{A,intra}$ and C_{eff} :

$$C_{eff} = \frac{K_{intra}}{K_{A,inter}} \quad C_{eff,ITC} = 22 (+26/-10) \text{ mM}$$

Geometric Approach

After the first bond forms, the remaining binding groups are confined within a characteristic distance r. An RDKit conformer search was used to estimate this distance.



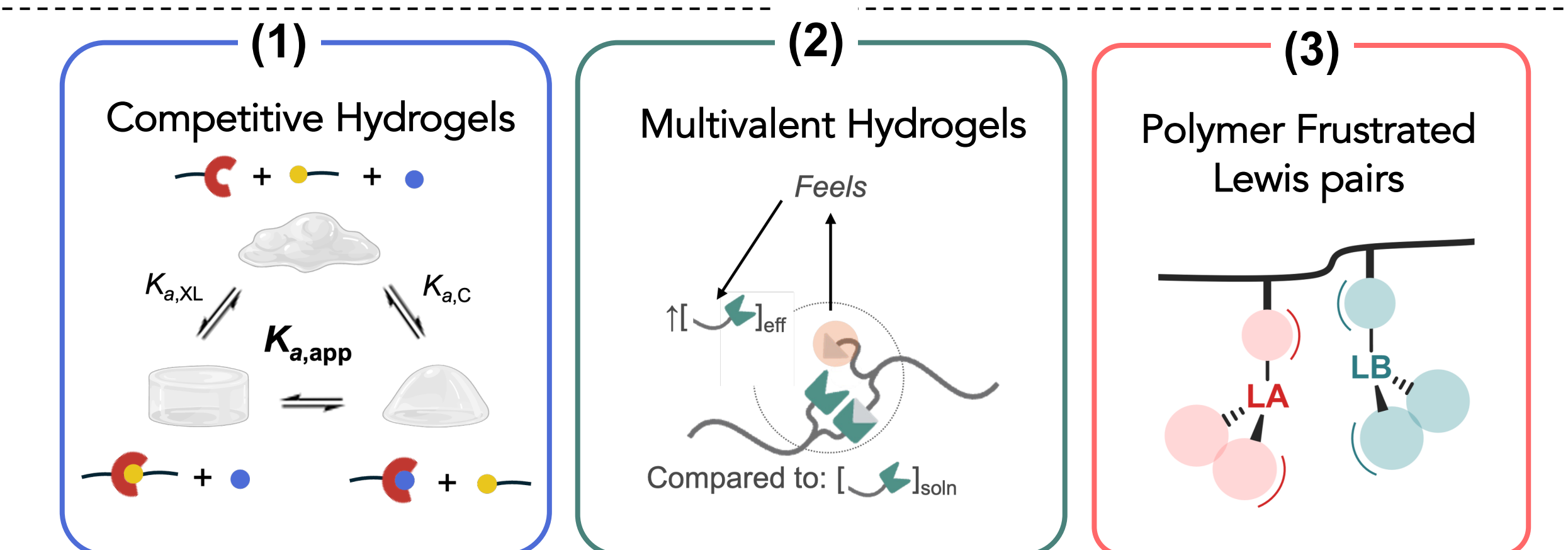
The Boltzmann-weighted mean separation was $r=23.15 \text{ \AA}$. Approximating the accessible volume as a sphere gives:

$$C_{eff} = \frac{1 \text{ molecule}}{\frac{4}{3}\pi r^3} = 32.5 \text{ mM}$$

Key Result

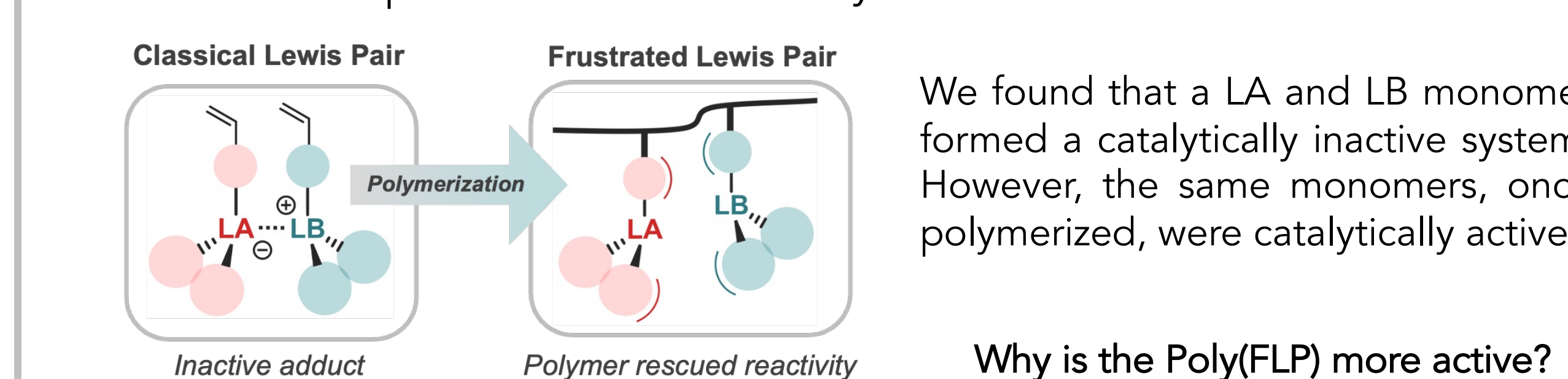
We propose that the relaxation time switching point (32.6 mM) can be approximated with two different independent methods of calculating effective concentration.

Want to learn more?
Contact Megan Rothenberg:

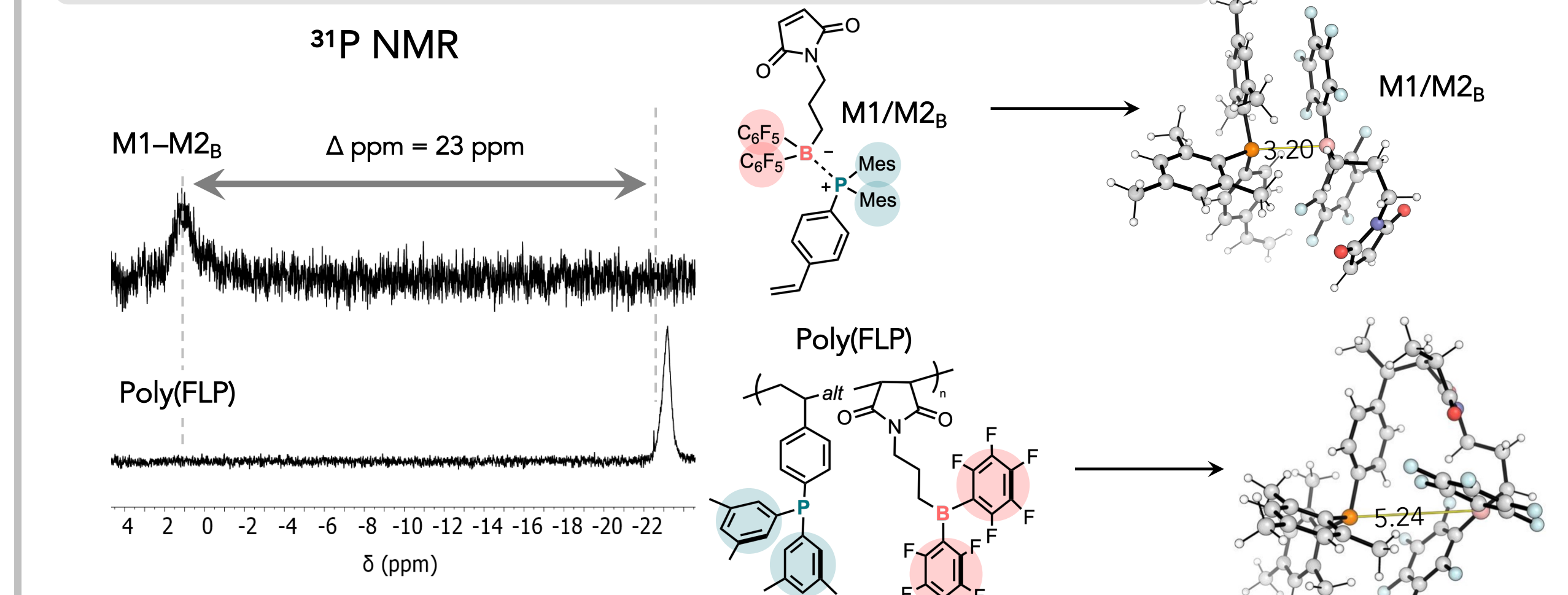


Polymer Supported Frustrated Lewis Pairs

Purpose: To determine how polymer backbone architecture creates frustrated Lewis pairs and enables catalysis.

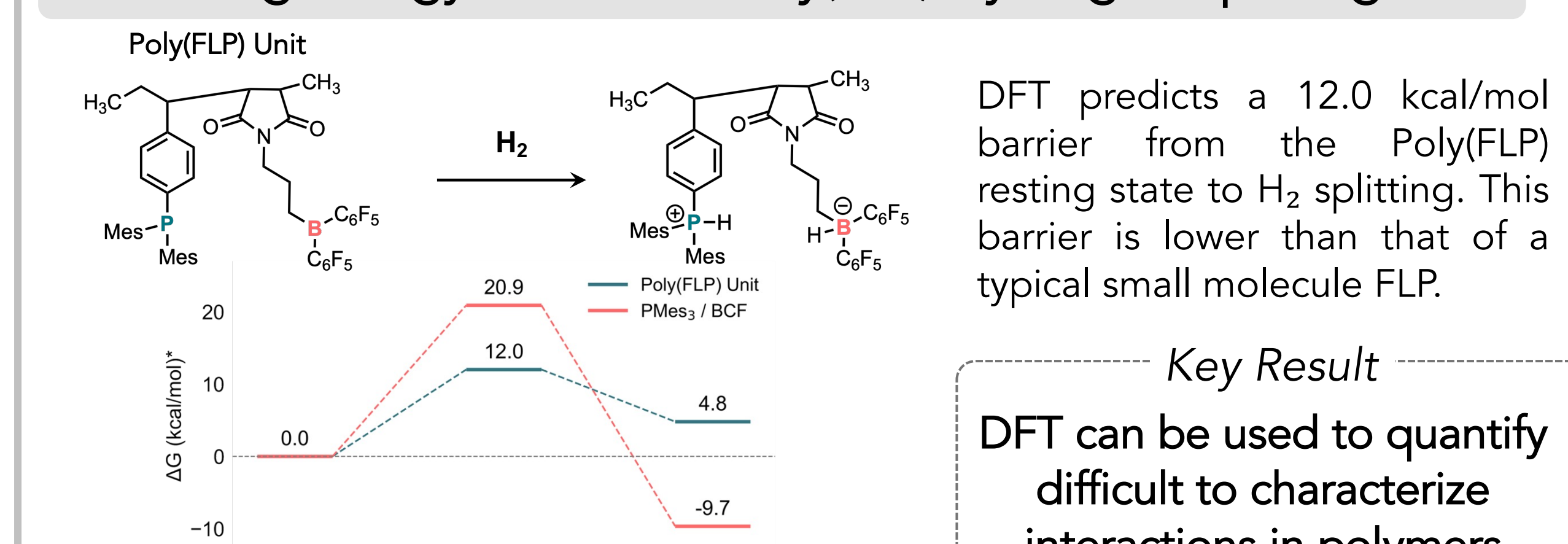


Experimental Observation of FLP Association

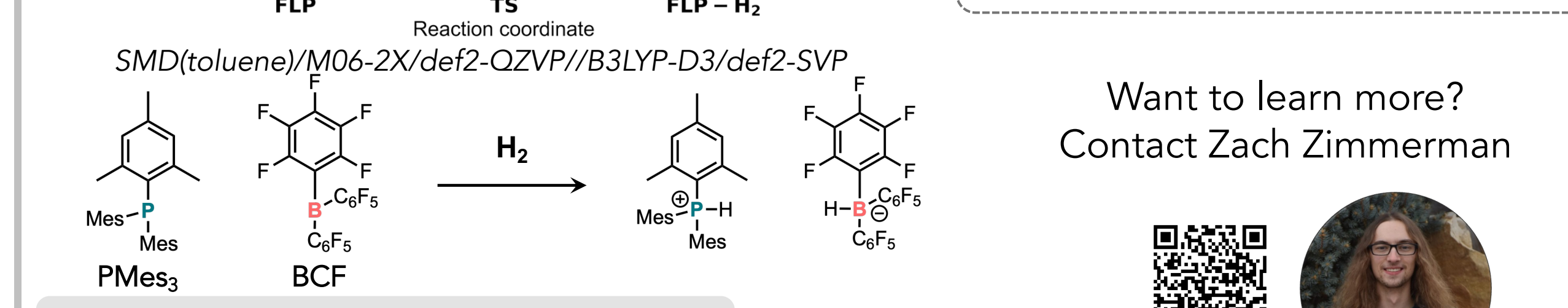


^{31}P NMR shows a 23 ppm shift upon polymerization, consistent with loss of Lewis acid-base association. MLIP sampling and DFT reproduce this shift ($\Delta\delta_{\text{calc}}=21.5 \text{ ppm}$) and predict that the B-P distance increases from 3.20 to 5.24 Å, supporting backbone-induced frustration.

Evaluating Energy Barrier for Poly(FLP) Hydrogen Splitting



DFT predicts a 12.0 kcal/mol barrier from the Poly(FLP) resting state to H_2 splitting. This barrier is lower than that of a typical small molecule FLP.



Acknowledgements

The Hill Group: Dr. Megan Hill, Dr. Sirilak Mekcham, Dr. Owen Lee, Dr. Lance P. Go, Ally Cunningham, Zach Zimmerman, Megan Rothenberg, Elizabeth Thompson, Macioe Firsching, Adelle Kirshner, Atlas Quaine, Elayna King, Gus Miller, Alex Bailey, Anna Miller

Funding: The Boettcher Foundation, ACS PRF

Want to learn more?
Contact Zach Zimmerman

