1-1-2014

The Use of Molecular Dynamics to Predict the Stability of Squaraine Rotaxanes

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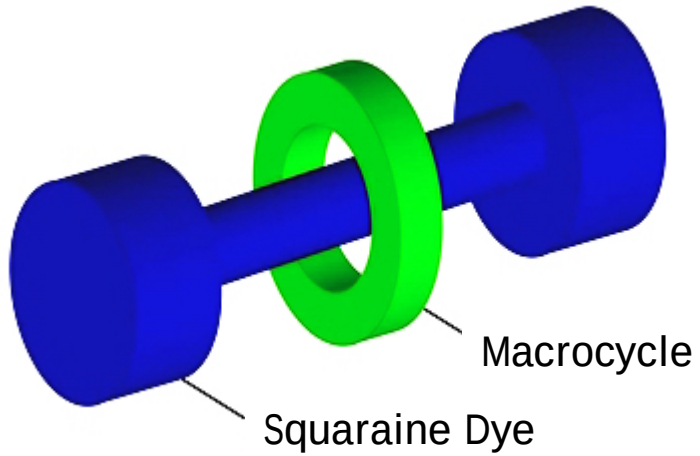
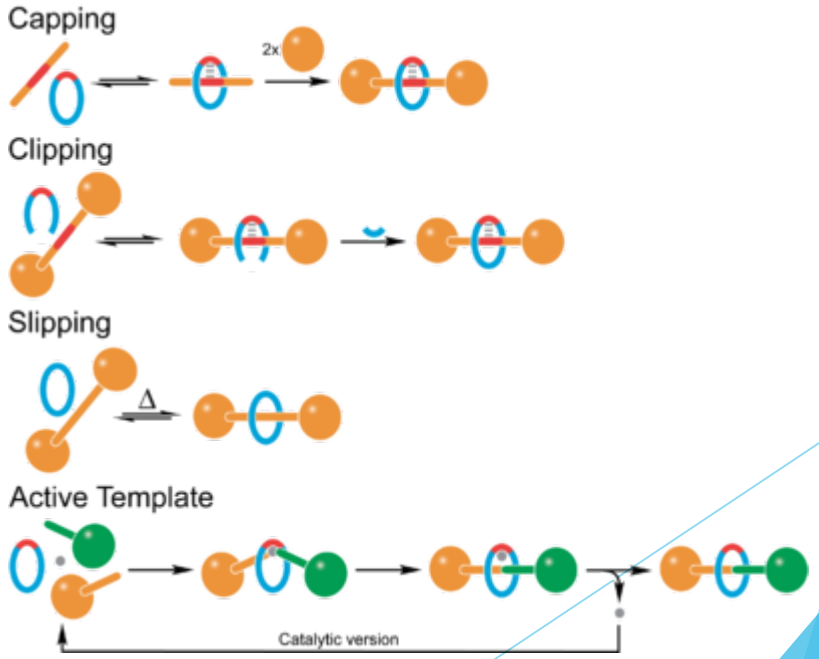
What is a Rotaxane?

- Generic shape
- Mechanically interlocked
  - Hydrogen bonds between squaraine dye and macrocycle
  - Size of endcaps prevents slipping
- Four main methods for synthesis
  - Capping
  - Clipping
  - Slipping
  - Active template
    - a.k.a. Leigh-type templating reaction



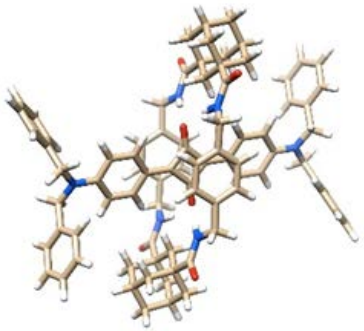


Properties

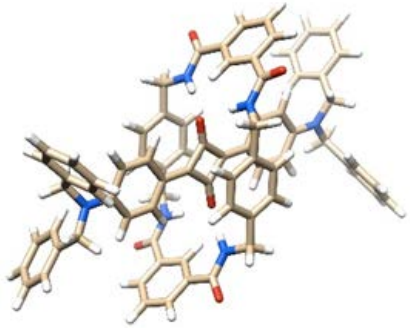
- Fluorescent dye
  - Can stain cancer cells, bacterial cells, etc.
- Absorbs near-infrared radiation
  - Can easily penetrate skin and tissue
- Washes out of samples easily if needed
- Can be used as molecular machine
  - Shuttles, switches, etc.

Previous Studies

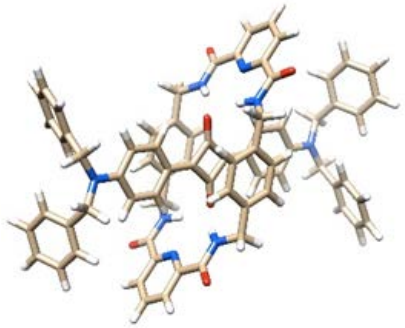
- Smith Group at the University of Notre Dame



Adamantyl Rotaxane

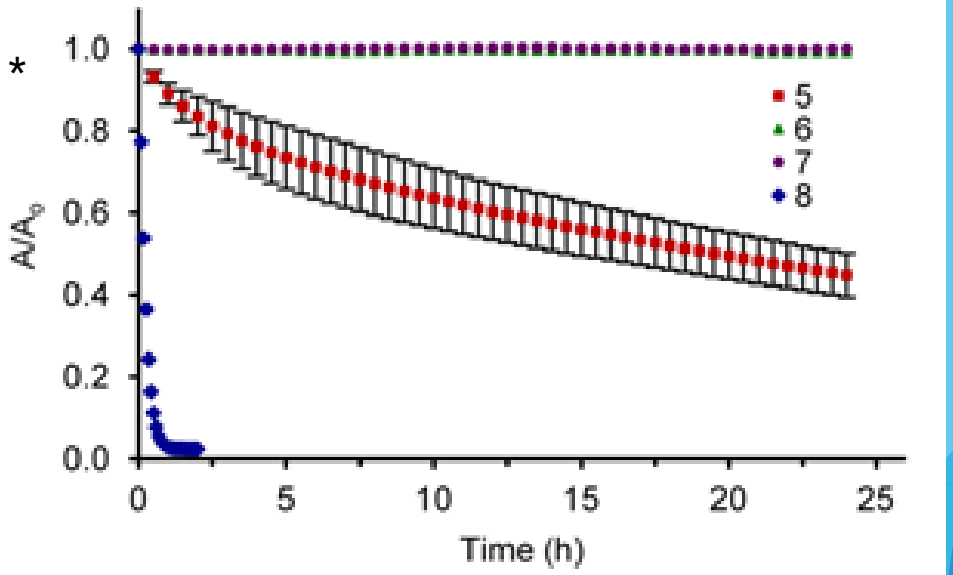


Isophthalamidyl Rotaxane



Pyridinyl Rotaxane

= free squaraine dye



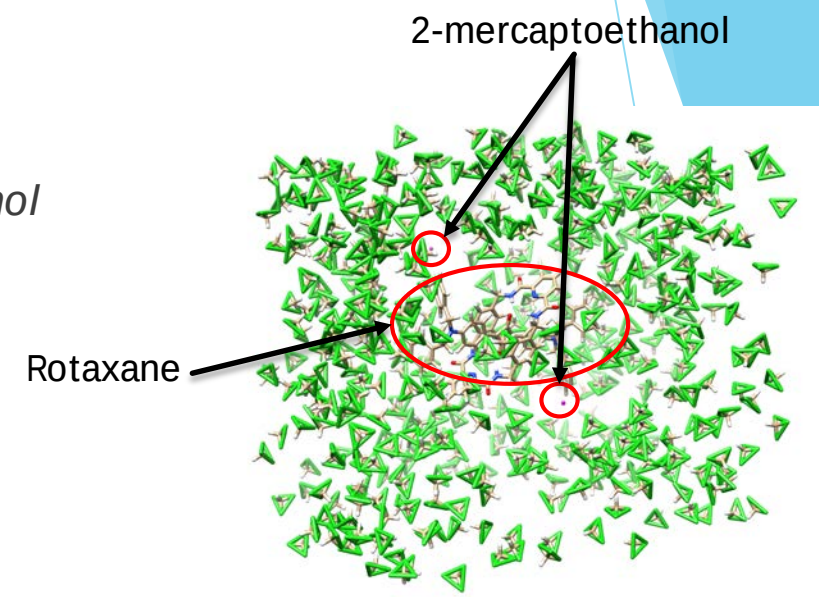
* Collins, C. G.; Johnson, A.; Connell, R. D.; Nelson, R.; Murgu. I.; Oliver, A. G.; Smith, B. (Unpublished work).

Methods

- Minimize the structure of each rotaxane
- Implicit solvent
  - Proof of concept study
  - Born implicit solvation model, dielectric constant of chloroform used ($\varepsilon = 4.81$)
  - Cutoff = 20 Å
  - 100 ns molecular dynamics (MD) trajectories
    - 1 fs timestep
  - Create histograms

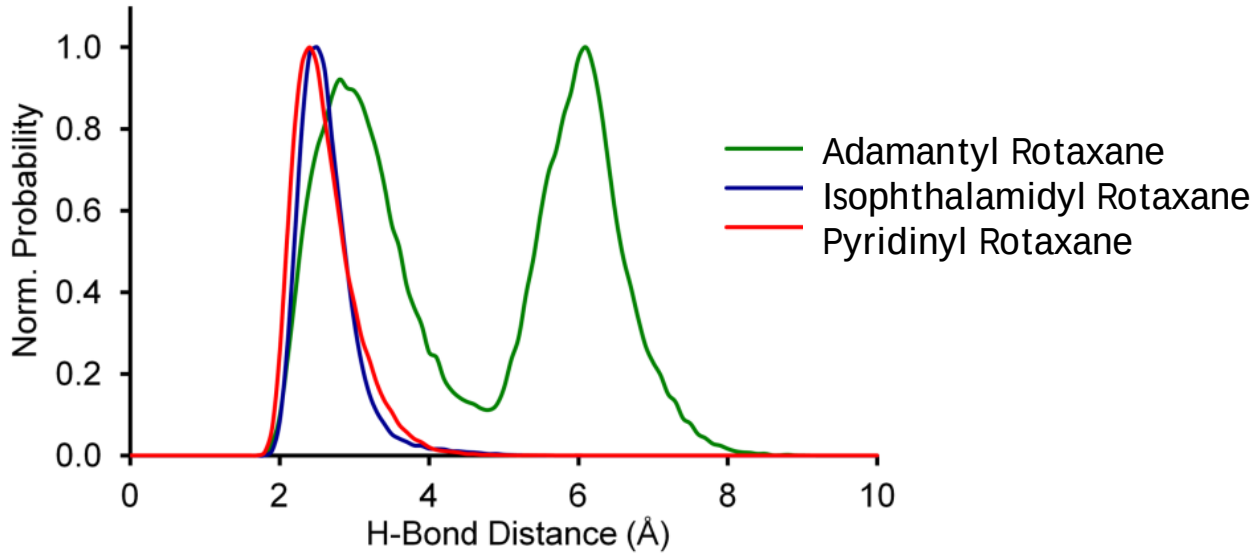
Methods

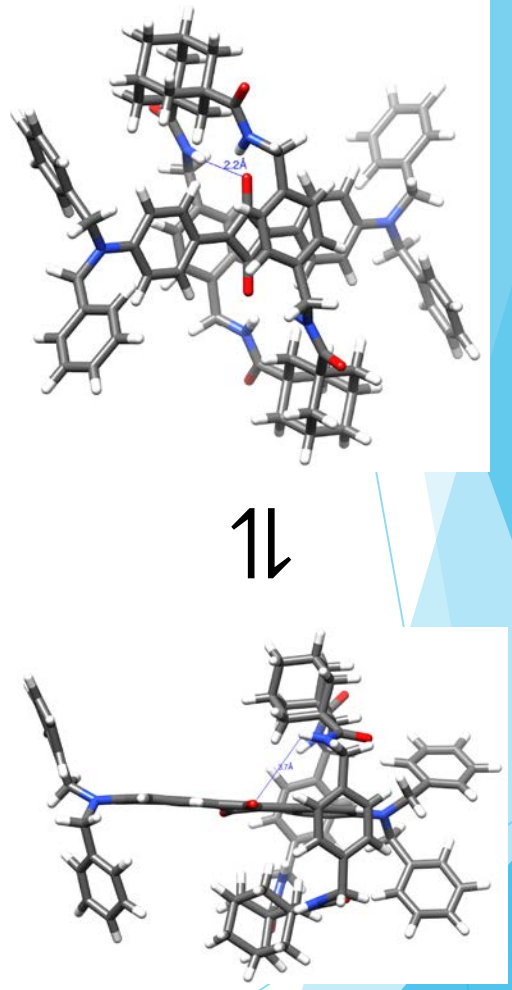
- Explicit solvent
  - Solvate each rotaxane in box of chloroform using *Packmol*
  - 2 molecules of 2-mercaptoethanol added
    - 5 μM concentration
  - Minimized solvent while constraining solute
  - Unconstrained minimization
  - Heat to 300 K while constraining solute
  - All constraints released, 200 ns MD trajectories
  - Create histograms



Rotaxane	Dimensions (Å)	Number of 2-mercaptoethanol molecules	Number of chloroform molecules
Adamantyl	47x43x36	2	538
Isophthalamidyl	47x39x35	2	481
Pyridinyl	47x40x35	2	491

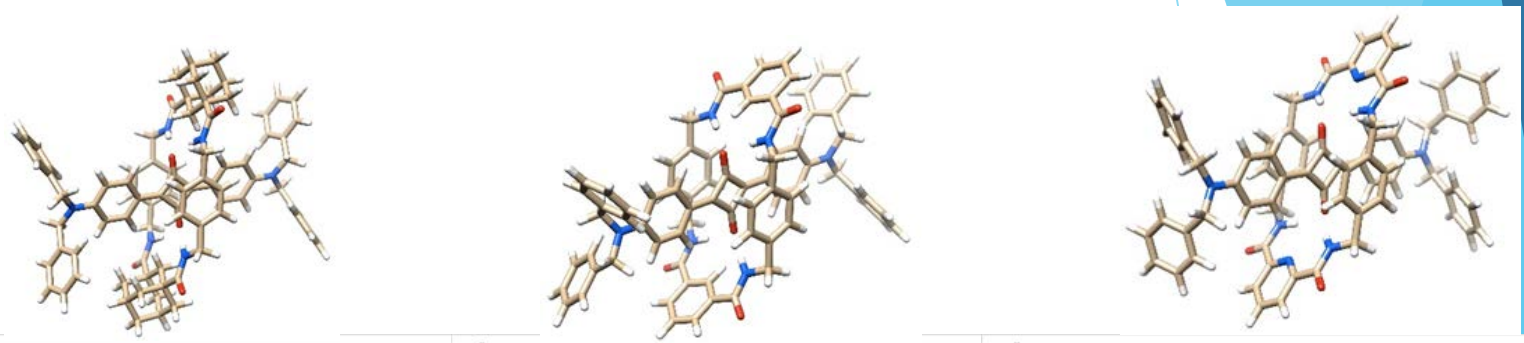
Results

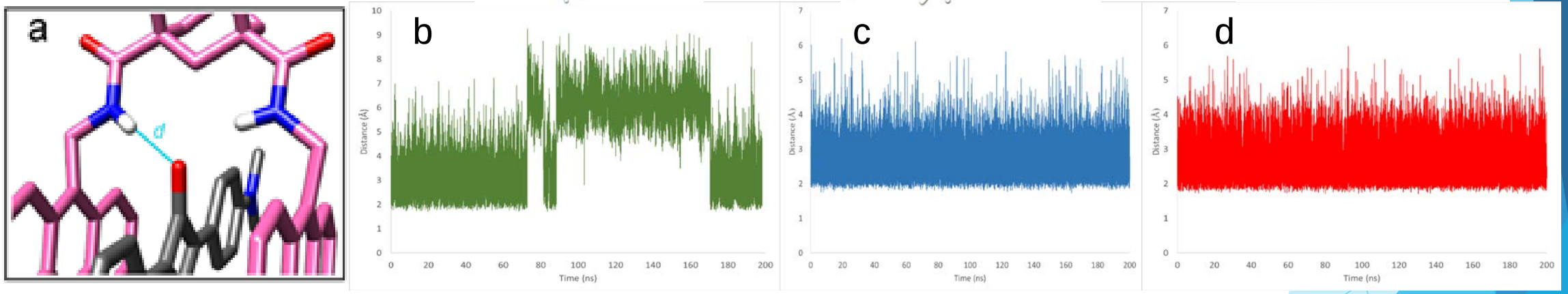




Normalized histogram of the hydrogen bond distances for each rotaxane

Results





(a) Hydrogen bond distance measured for each rotaxane
(b) Adamantyl hydrogen bond distance vs. time
(c) Isophthalamidyl hydrogen bond distance vs. time
(d) Pyridinyl hydrogen bond distance vs. time

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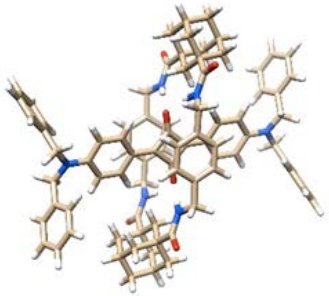
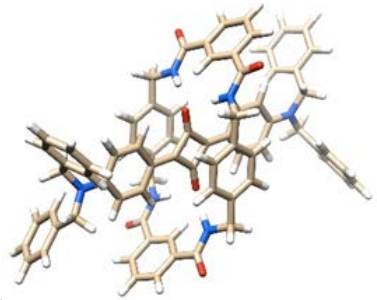
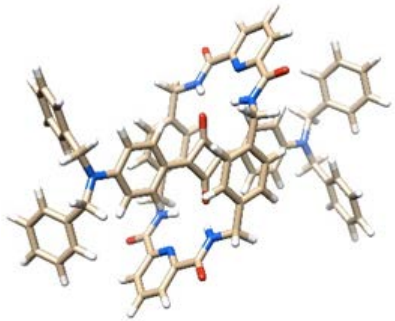
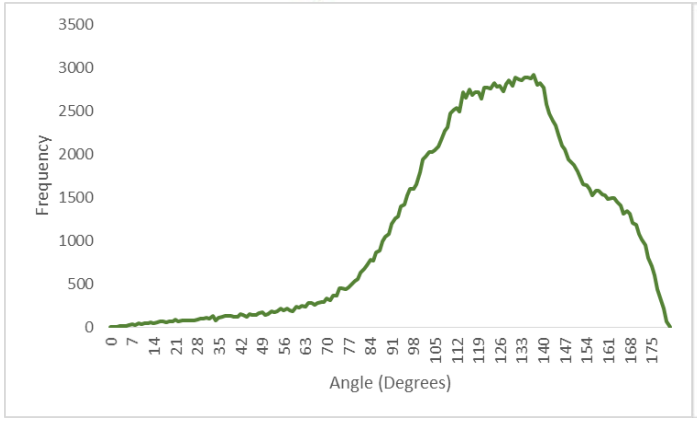
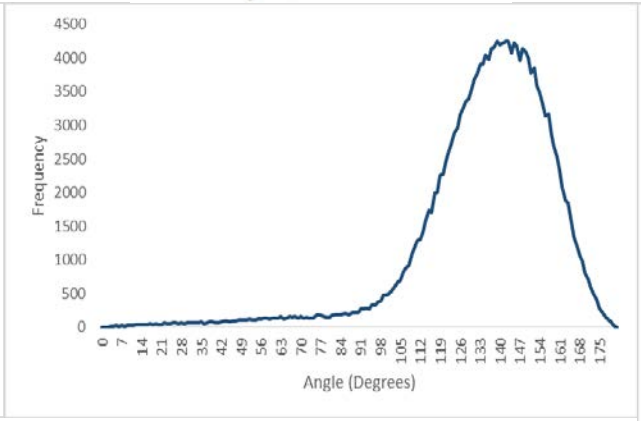
Results

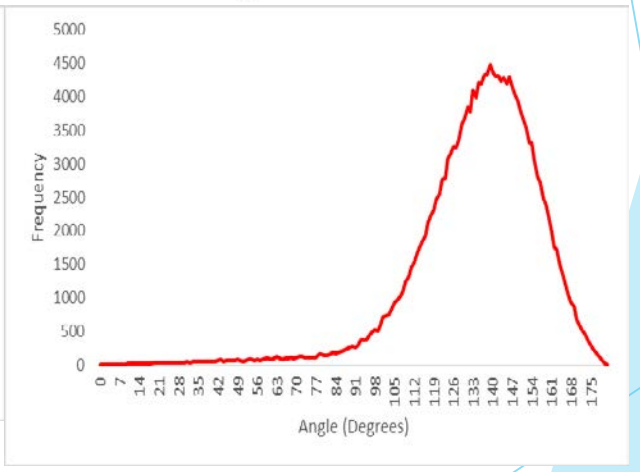






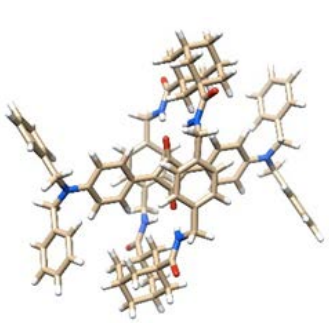


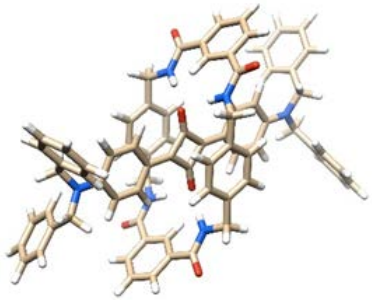


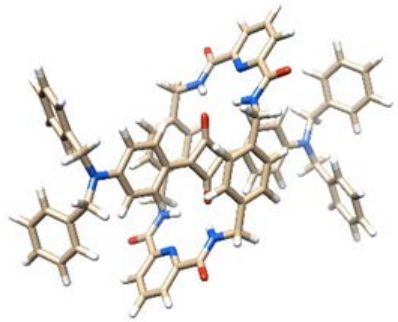


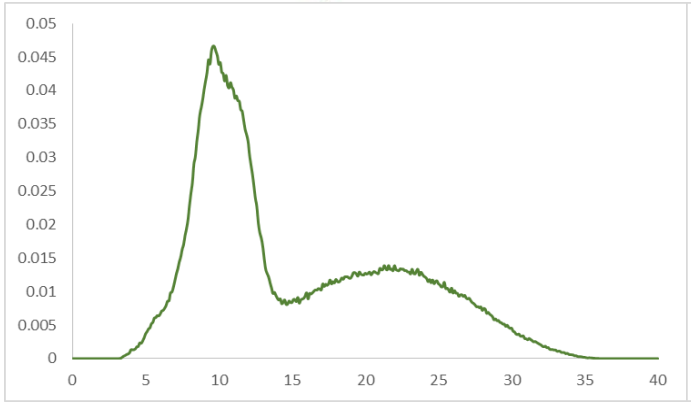
Squaraine-macrocycle angle vs. time for each rotaxane

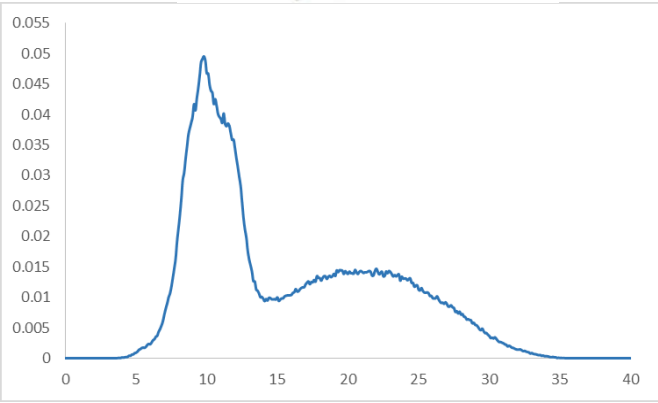
Results

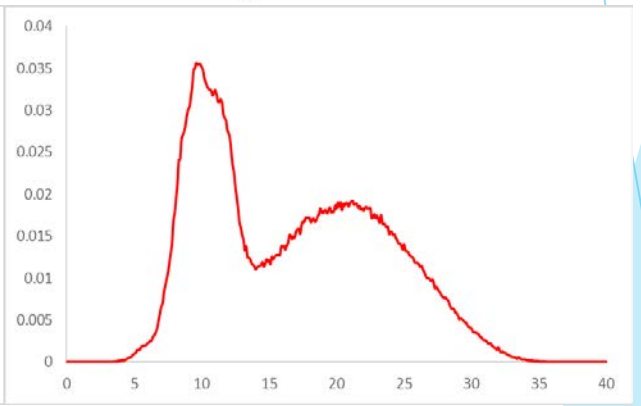












Sulfur-carbon distance vs. time

Conclusions

- Along with previous studies, our results show that isophthalamidyl and pyridinyl macrocycles can effectively protect squaraine dyes from nucleophilic attack
  - MD simulations show that squaraine does not slip out of these macrocycles
- Isophthalamidyl and pyridinyl macrocycles have many double bonds and are therefore conjugated
  - Higher rigidity does not allow squaraine dye to slip out
- Adamantyl macrocycle has fewer double bonds and is therefore not conjugated
  - Lower rigidity allows bond angles to rotate enough to let the squaraine slip through
- These methods can be used in the future to help design new rotaxanes
  - Future of biomedical imaging probes?

Acknowledgements

- Dr. Andrew Johnson
- The Smith Group at the University of Notre Dame
- Concordia University
- Oregon Academy of Sciences

The Smith Group