1-1-2016

A Comprehensive Exploration of the Conformational and Energetic Landscape of a Rotaxane System: A Molecular Dynamics Study

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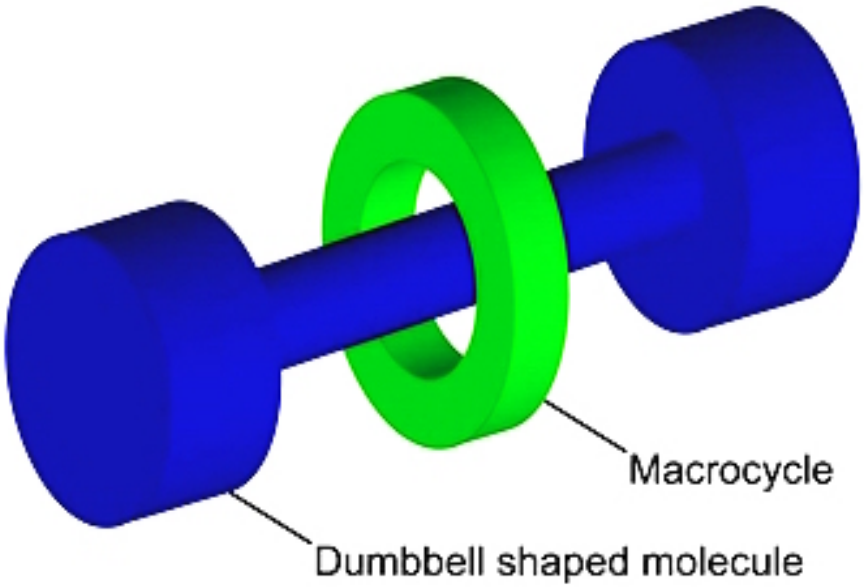
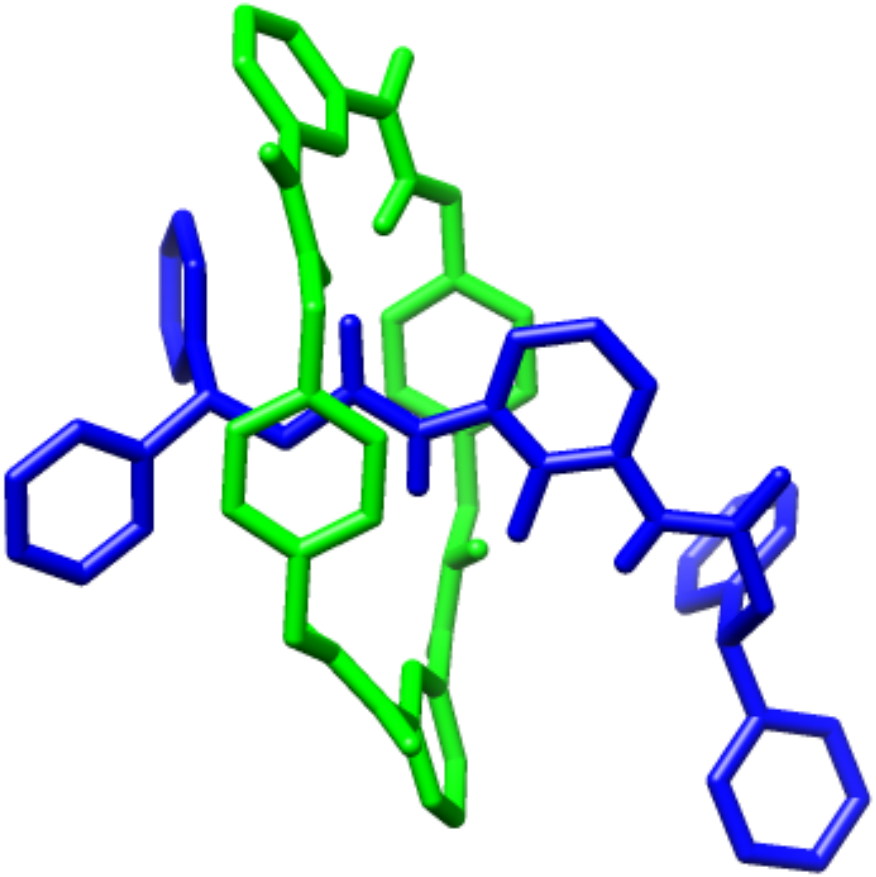
Ken Bodzewski

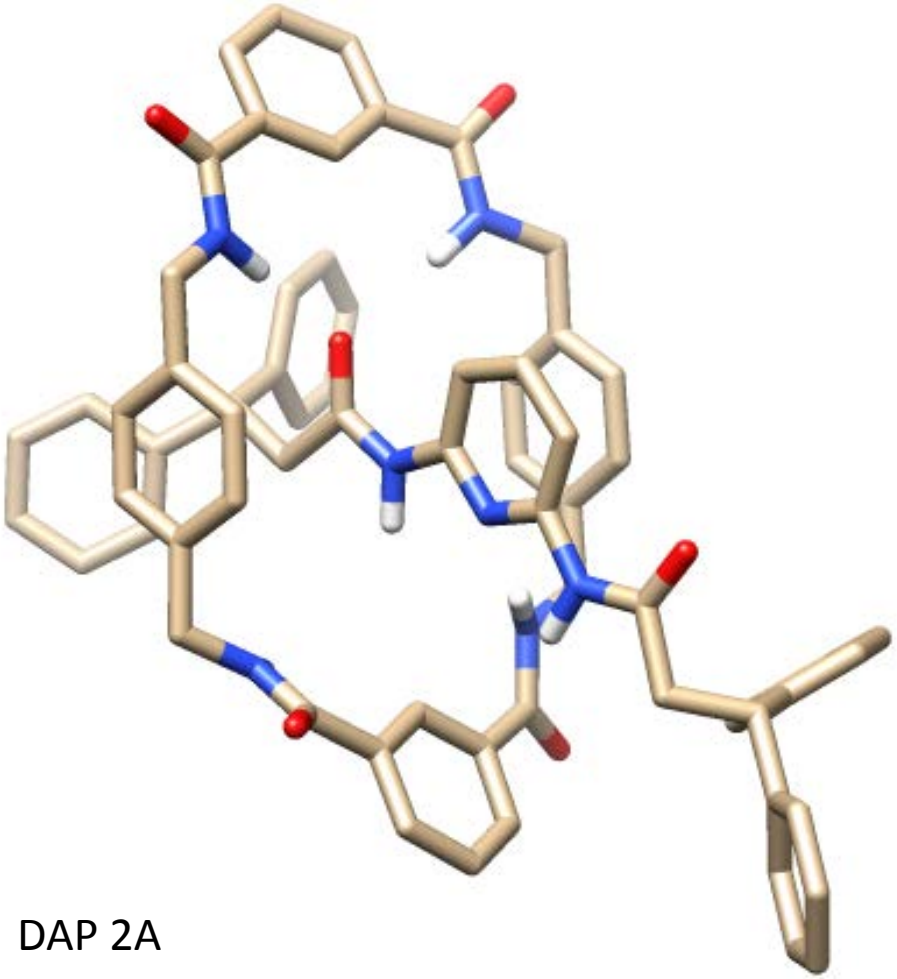
Rotaxanes



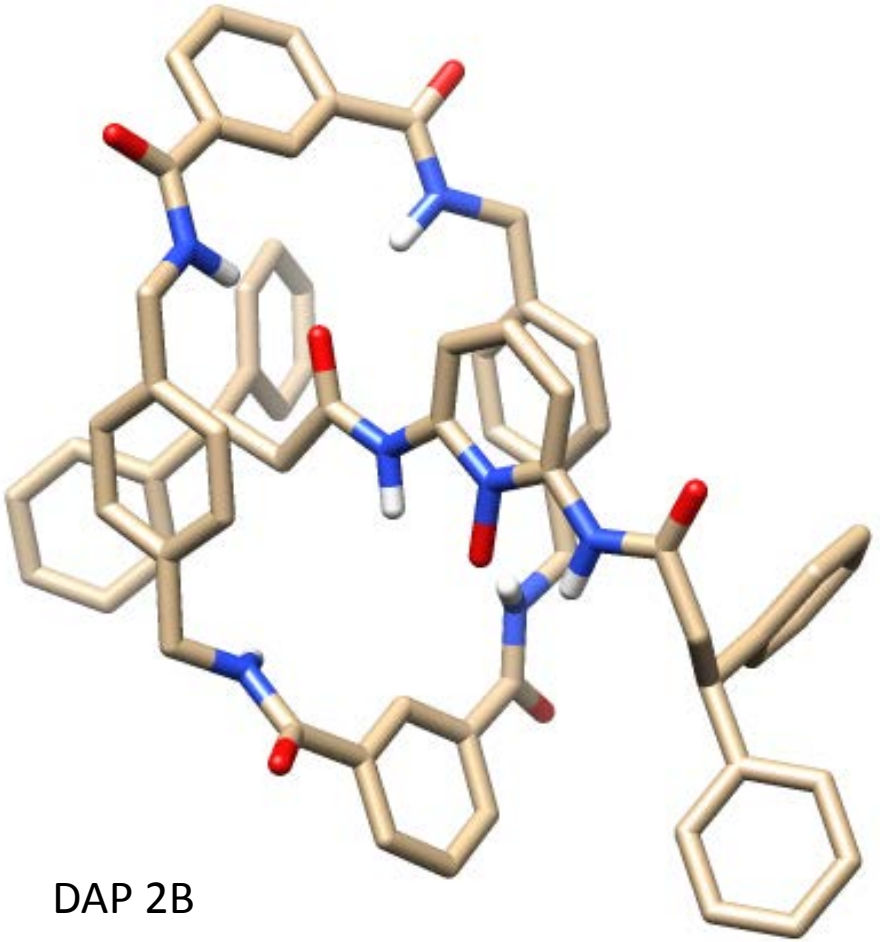


(Rotaxane. (2015, September 7). In *Wikipedia, The Free Encyclopedia*. Retrieved 06:55, February 27, 2016, from https://en.wikipedia.org/w/index.php?title=Rotaxane&oldid=679901561)

Di(acylamino)pyridine (DAP) based rotaxanes



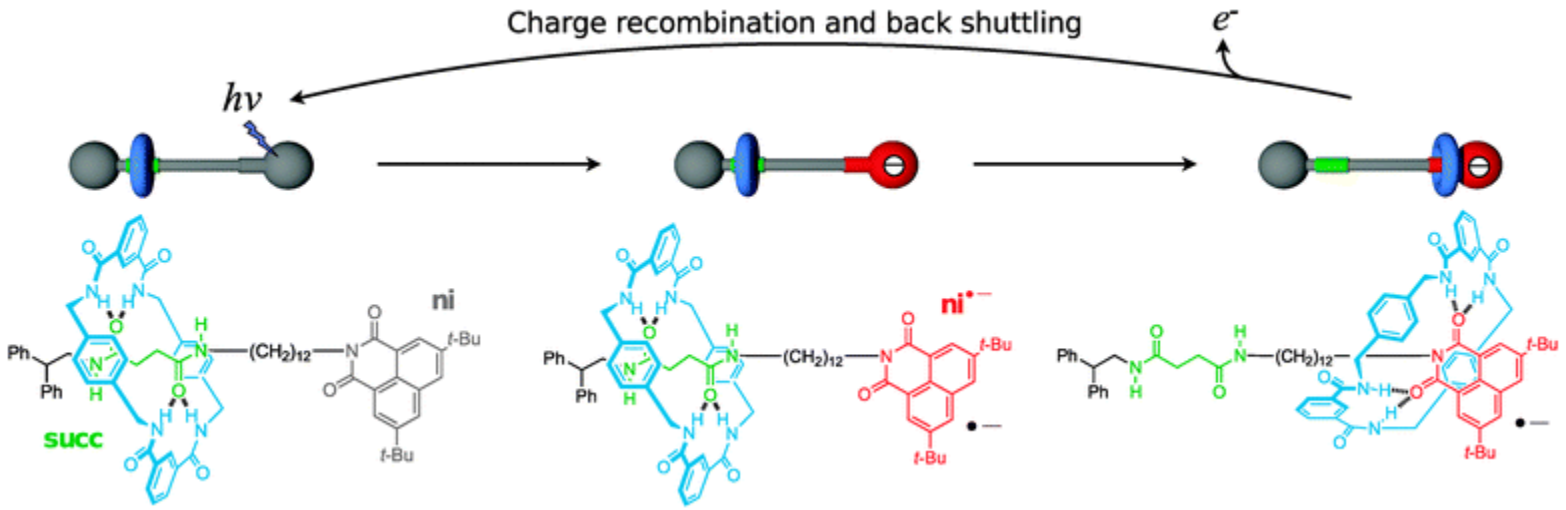
DAP 2A



DAP 2B

Relevance

- Rotaxanes are being used more and more.
  - Molecular machines.
    - Switches to turn them “on” and “off”
    - Rotation is often paired with a sliding or “shuttling.”

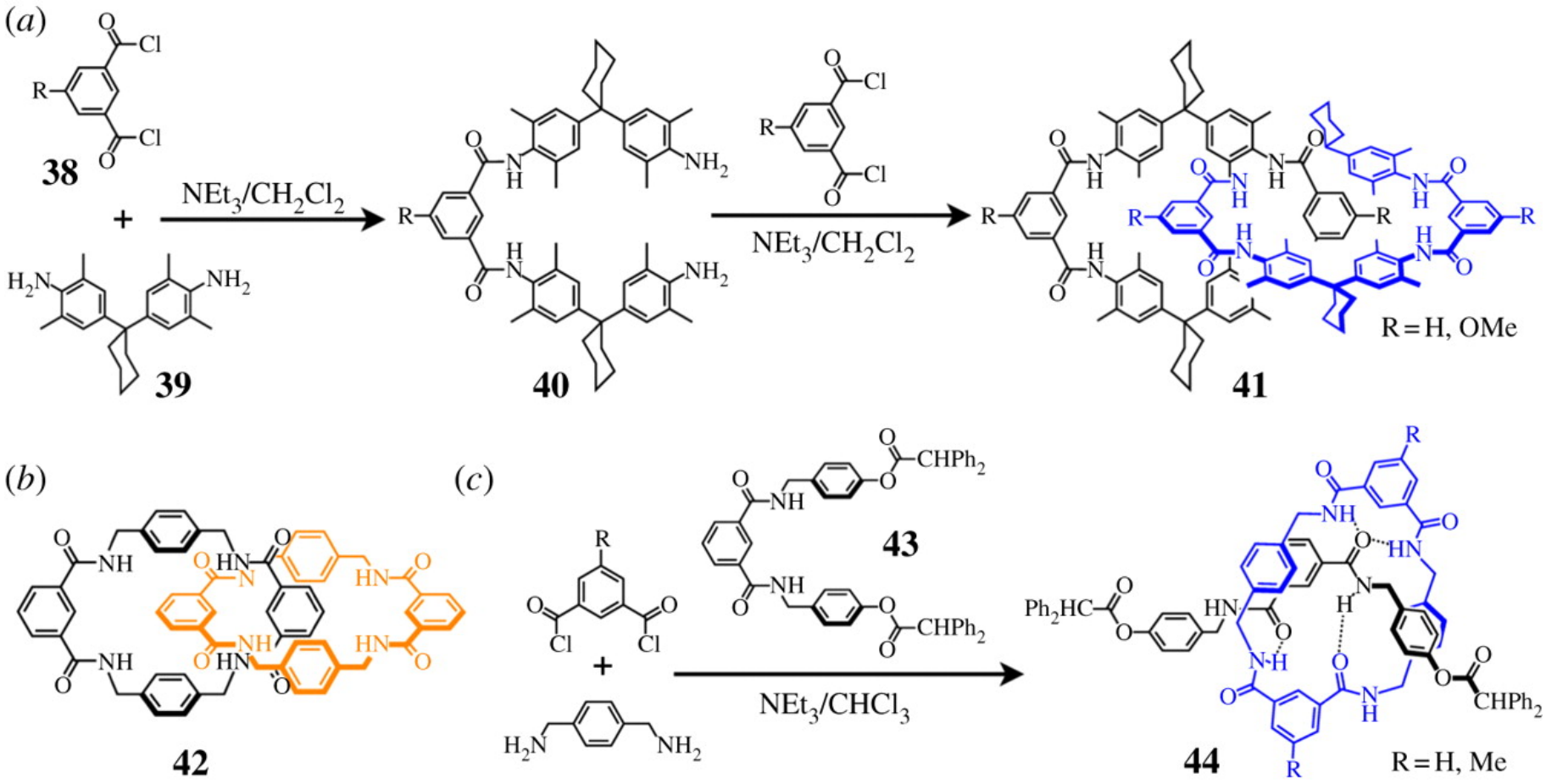


(Matthijs R. Panman, et al. Time-resolved vibrational spectroscopy of a molecular shuttle, *Phys. Chem.* 14, 2014)

Relevance

- Very difficult to make, low yield.
  - Molecular Dynamics as a way to study them before synthesizing them.
    - Use it as a predictor for how your rotaxane will respond.

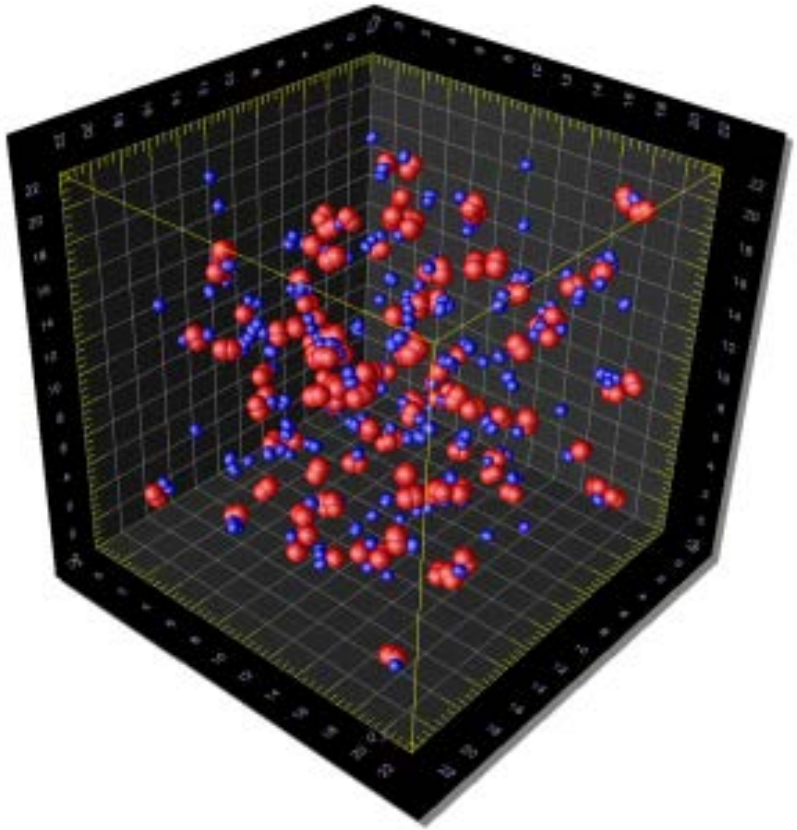
Relevance



(Gokhan Barin, Ross S. Forgan, J. Fraser Stoddart
Proc. R. Soc. A 2012 468 2849-2880; DOI: 10.1098/rspa.2012.0117. Published 24 August 2012)

Molecular Dynamics

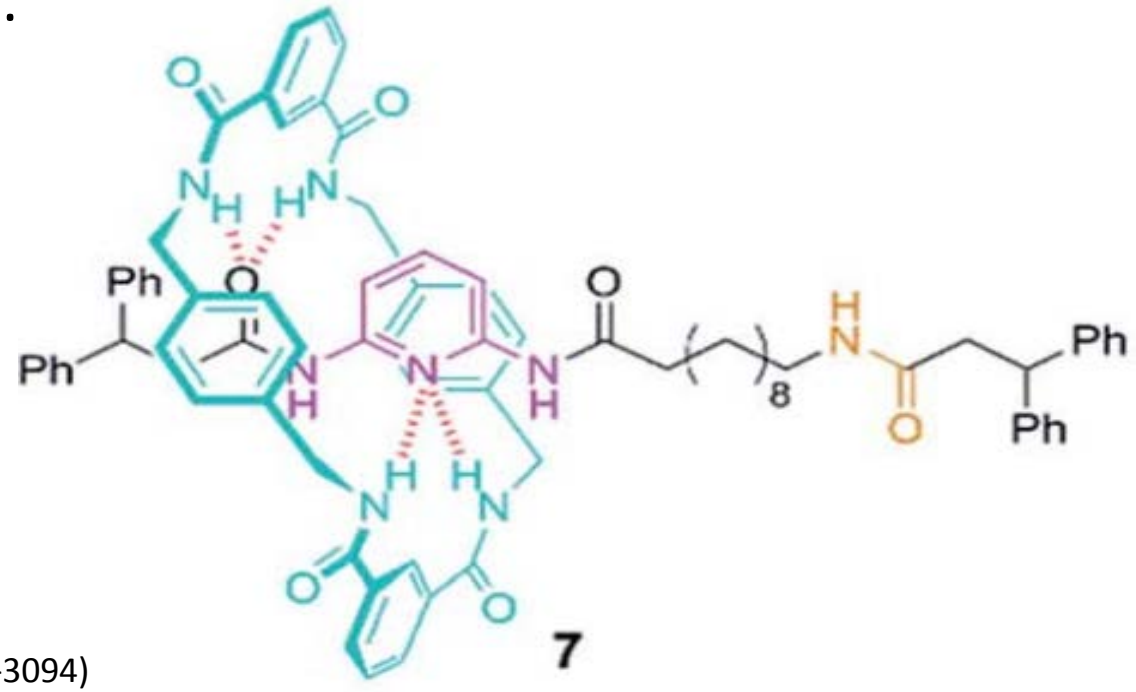
- Classical (Newtonian) mechanics.
- NAMD.
- VMD.
- Roughly 2,000 atoms in our systems.



(http://www.bgce.de/curriculum/projects/moldyn/)

Previous Study

- Used NMR spectroscopy to find energy required for rotaxane pirouette.
- Looked at three different rotaxanes.
  - We studied two of these three.
- Solvated in chloroform.



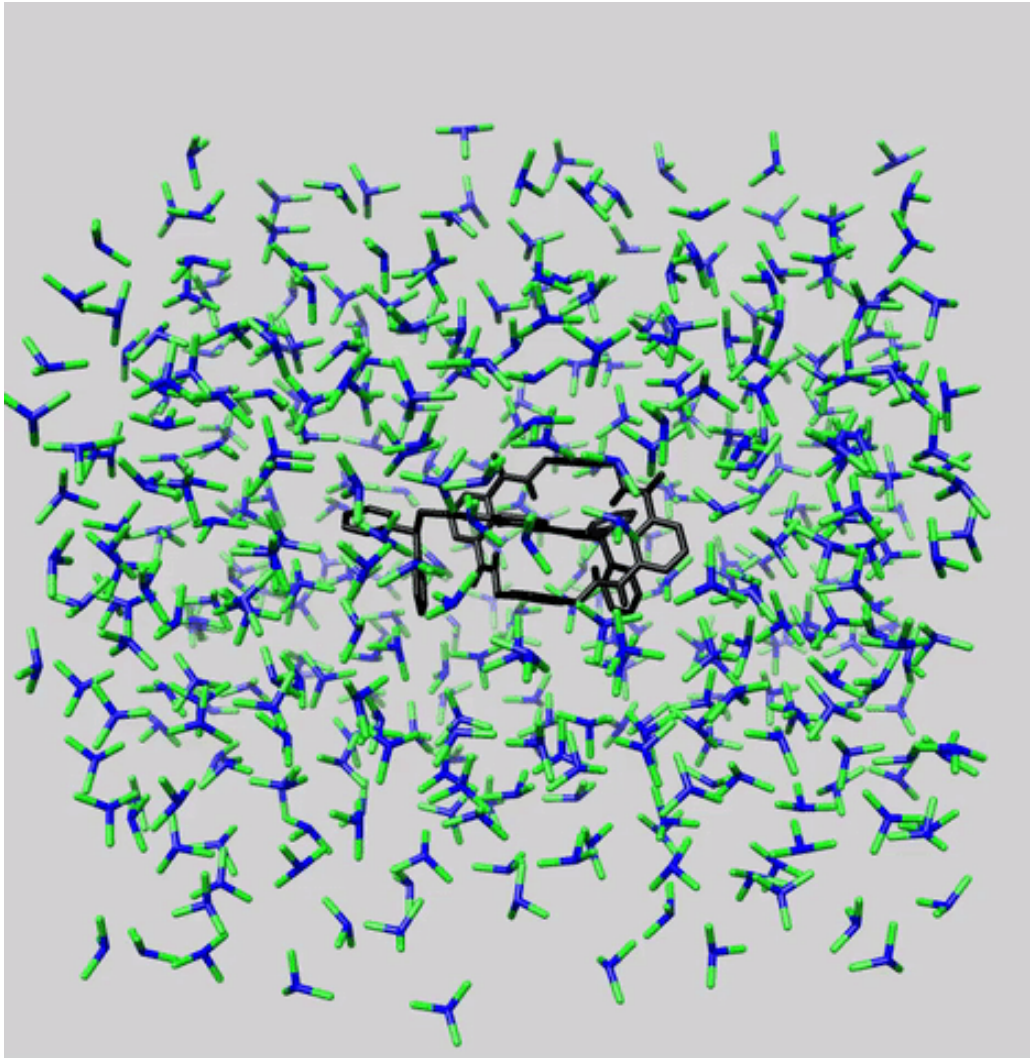
(Martinez-Cuezva, et al. *Chem. Sci.*, 2015, **6**, 3087-3094)

Procedure

- R.E.D.D. server to derive partial charges on our rotaxanes.
- System was created through the use of AmberTools.

Procedure

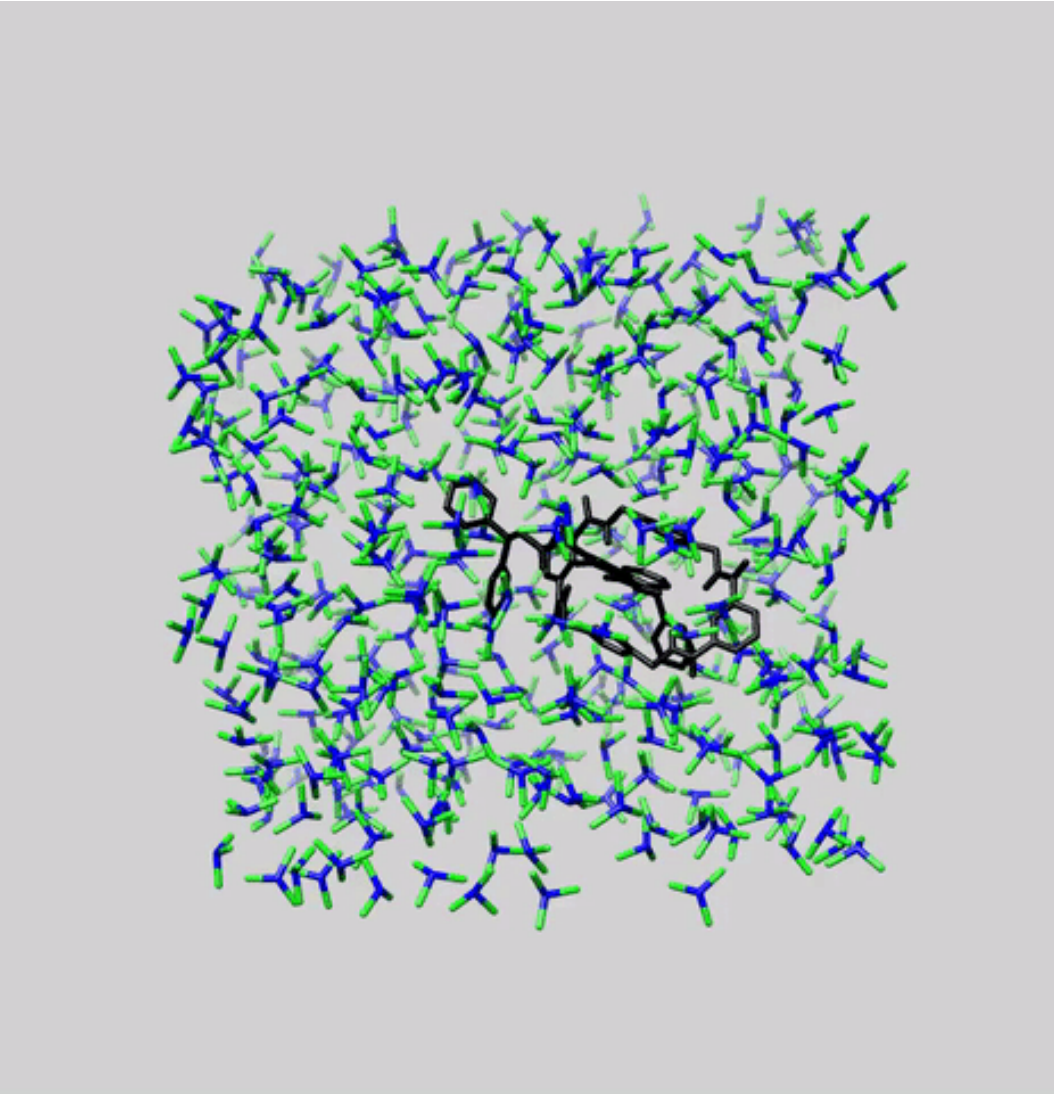
- Rotaxane held still while chloroform is relaxed.
- Whole system is relaxed.



(visualized with chimera)

Procedure

- Slowly heat up the system at constant volume.
- Equilibrate for 50 nanoseconds.

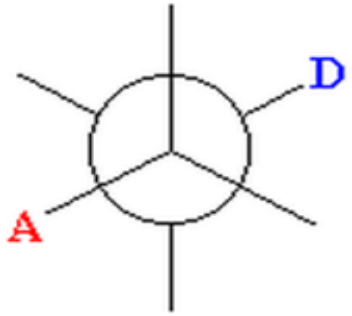


(visualized with chimera)

Dihedral Angle

- Angle made up of 4 atoms.
  - Created by first and fourth atom, second and third atom act as an axis.
- Defined three atoms on the thread and one on the macrocycle.
- Tried countless combinations.

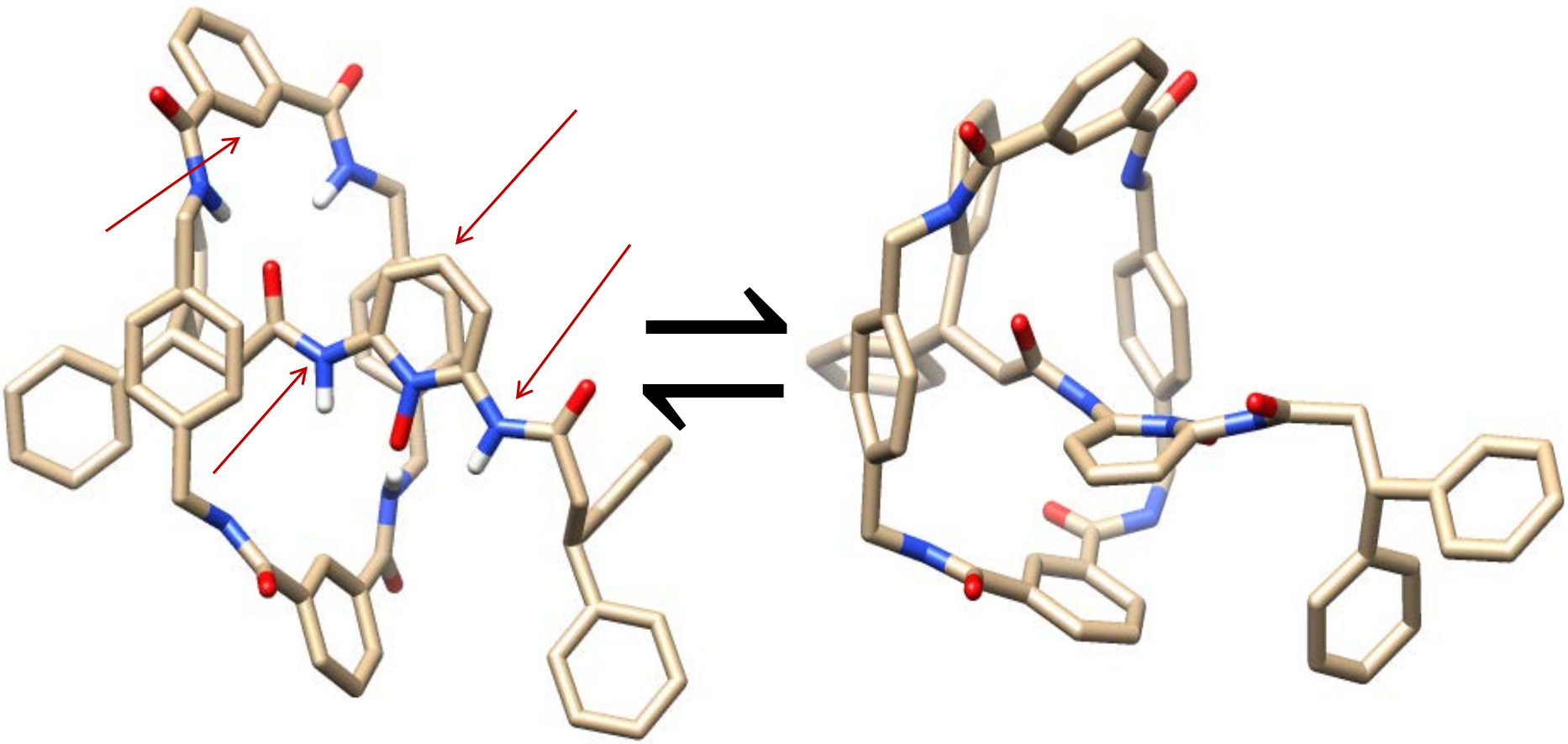
Sawhorse projection



Newman projection

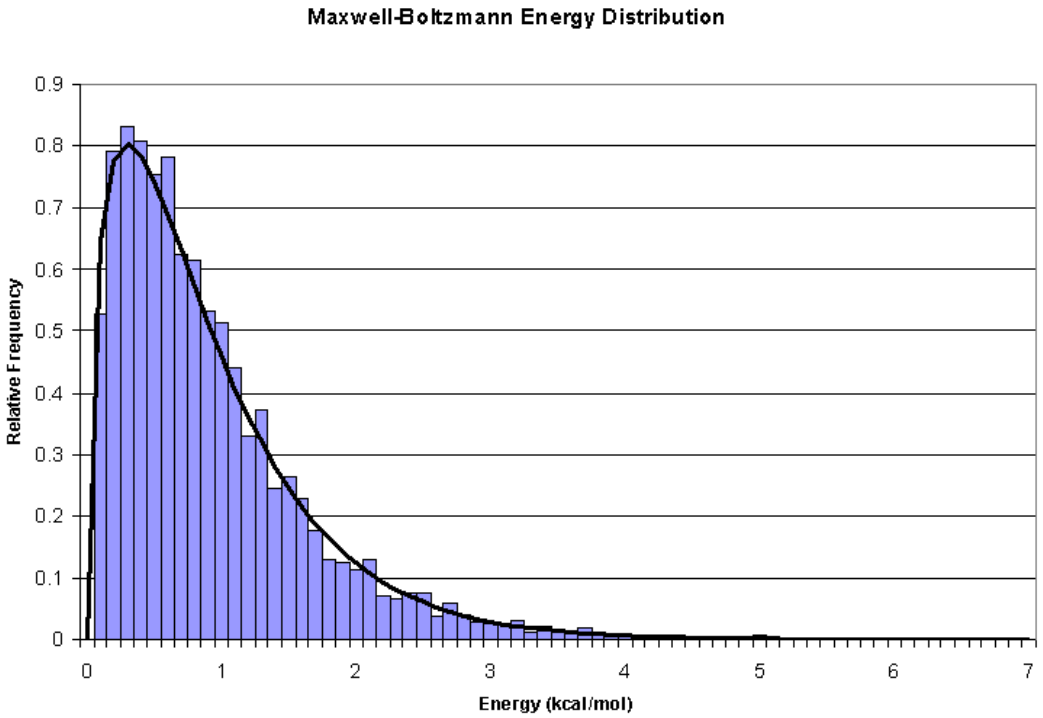
(http://tigger.uic.edu/~kbruzik/text/chapter6.htm)

Simulated Rotation



Biased Sampling

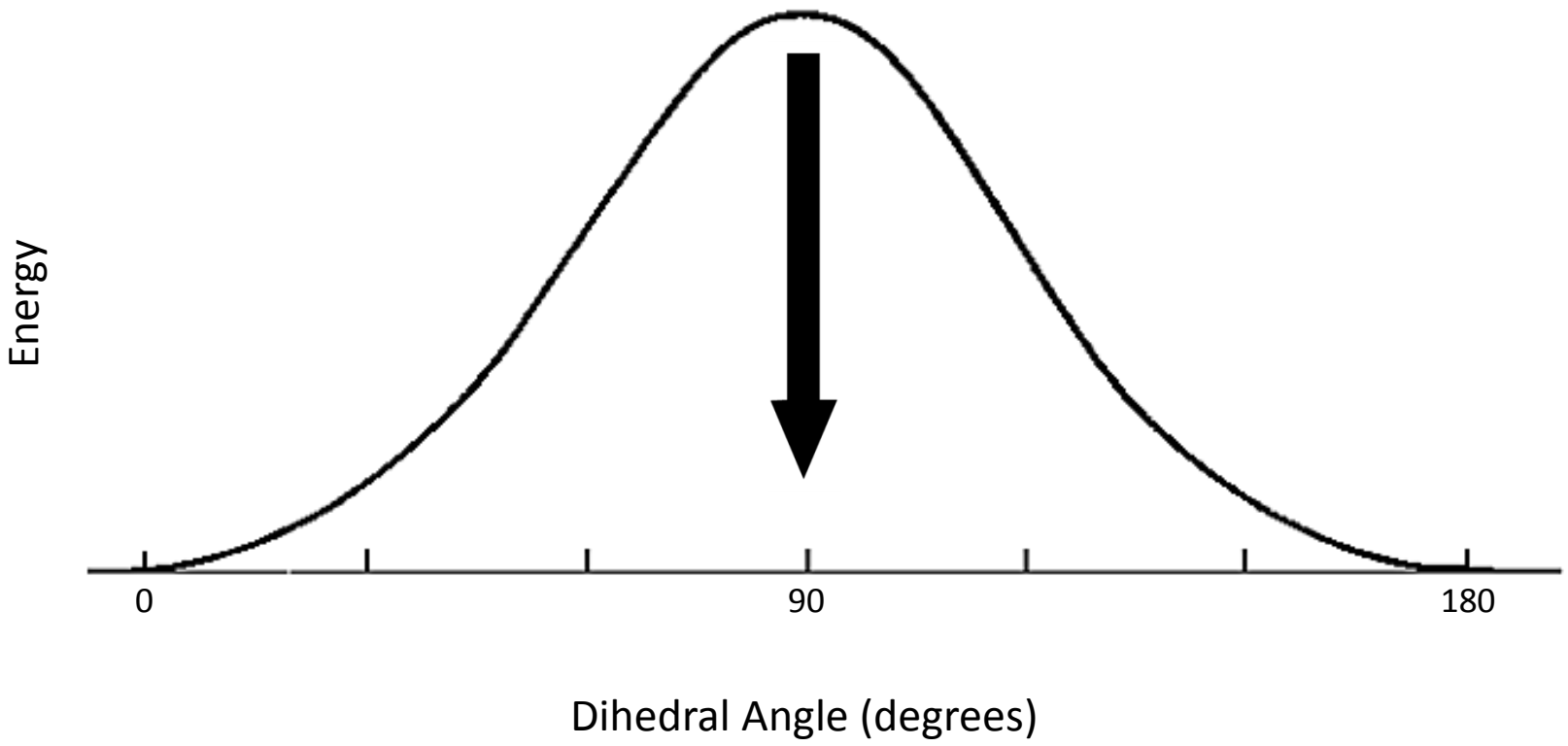
- Adaptive Biasing Force, Metadynamics, and Umbrella Sampling.
- Apply force on the system to allow molecules to go through otherwise unfavorable conformations.
- Took 3-4 hours to produce 1 nanosecond simulation.
- Much more efficient way of mapping free energy barriers.



(James C. Phillips, et al. Scalable molecular dynamics with NAMD. *Journal of Computational Chemistry*, 26:1781-1802, 2005.)

Adaptive Biasing Force

- Adaptive Biasing Force
  - Flattening out energy barriers to allow full sampling.



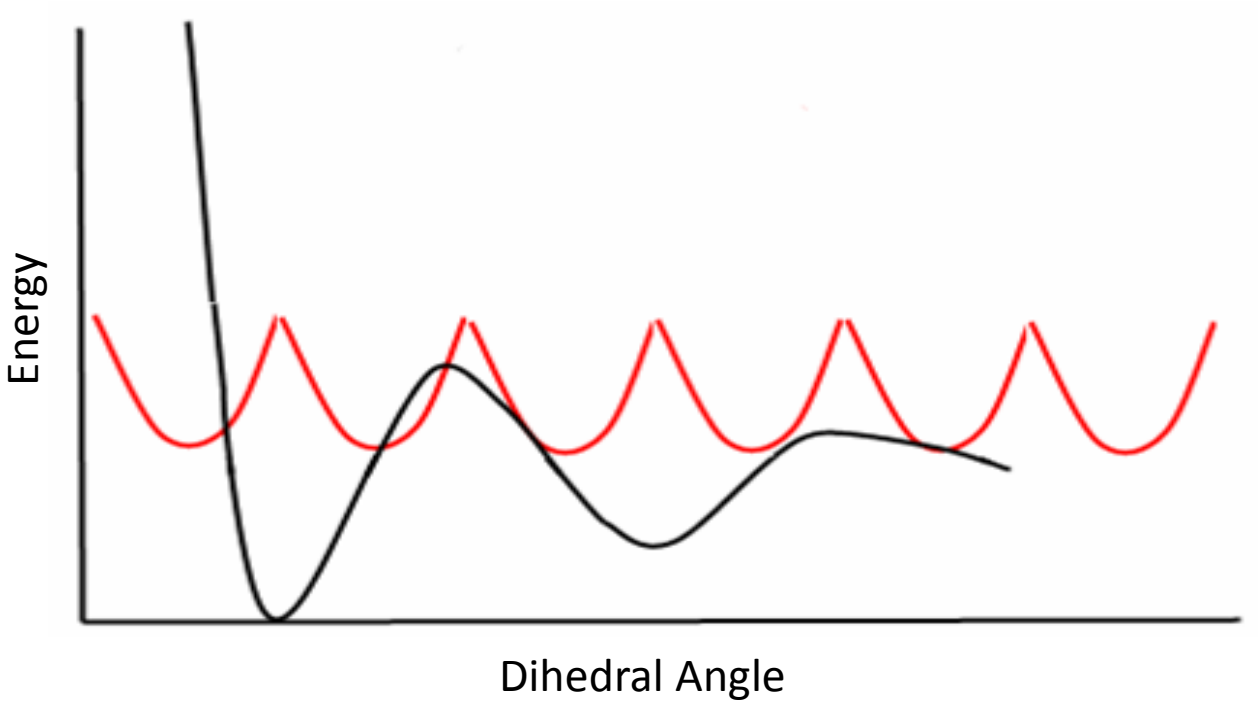
Metadynamics

- Metadynamics
  - Flooding low energy areas to fill up energy valleys.
- Allows for more sampling at high energy states.

(http://people.sissa.it/~laio/Research/Res_metadynamics.php)

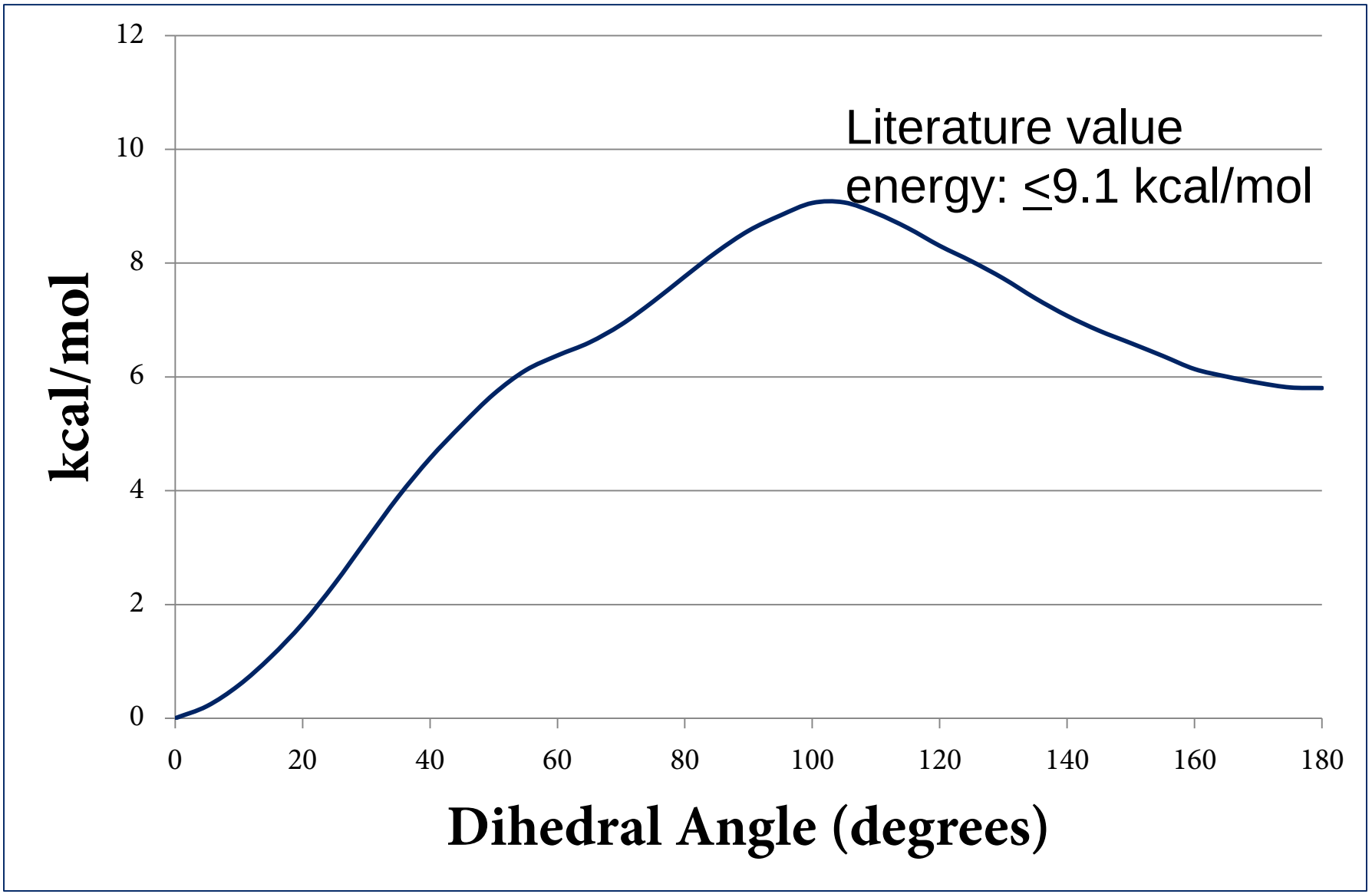
Umbrella Sampling

- Umbrella Sampling
  - Multiple runs held at different angle ranges.
    - 0 to 180 degrees, 5 degrees apart.

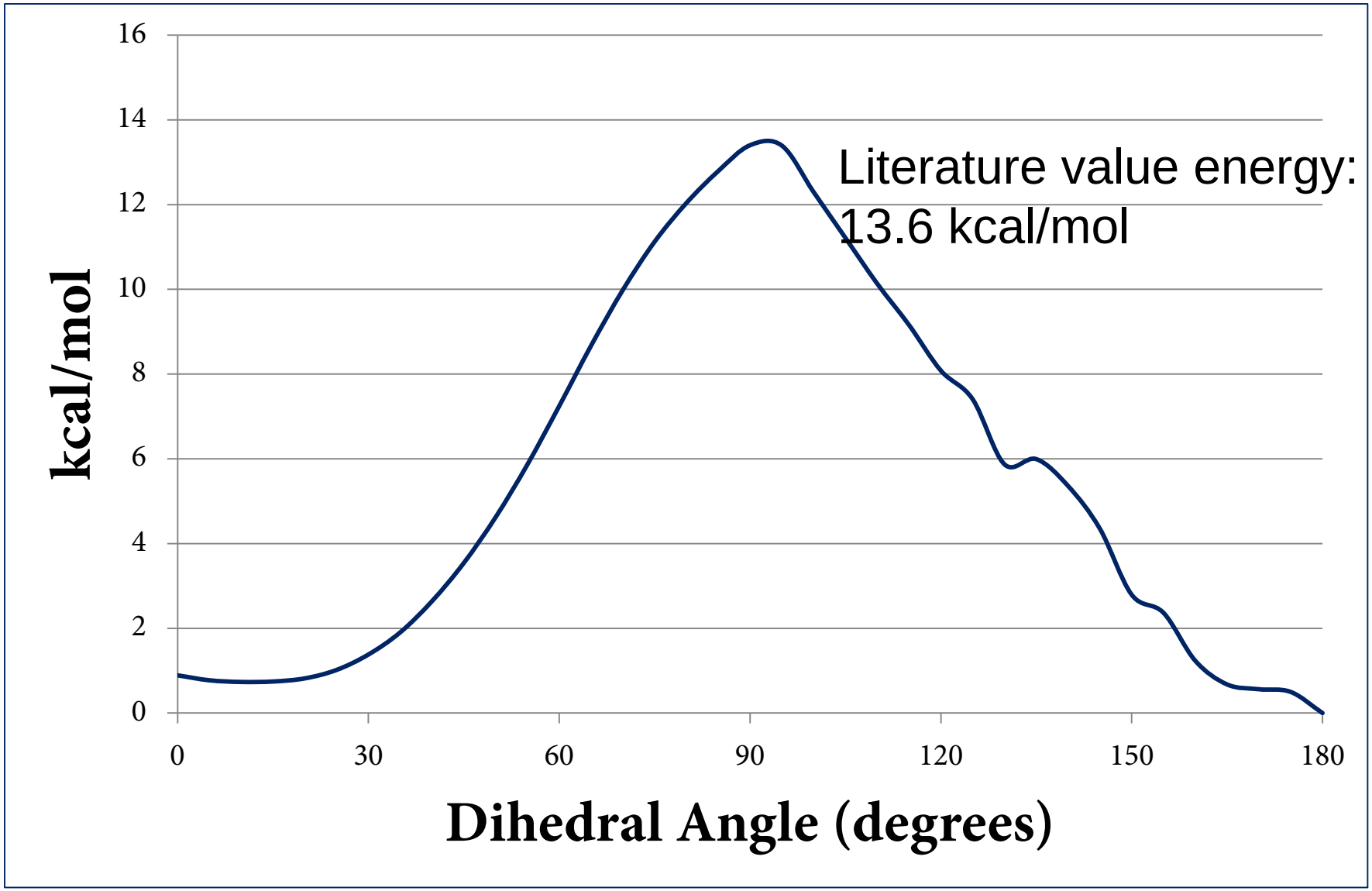


(http://w3.iams.sinica.edu.tw/lab/jlli/thesis_andy/node17.html)

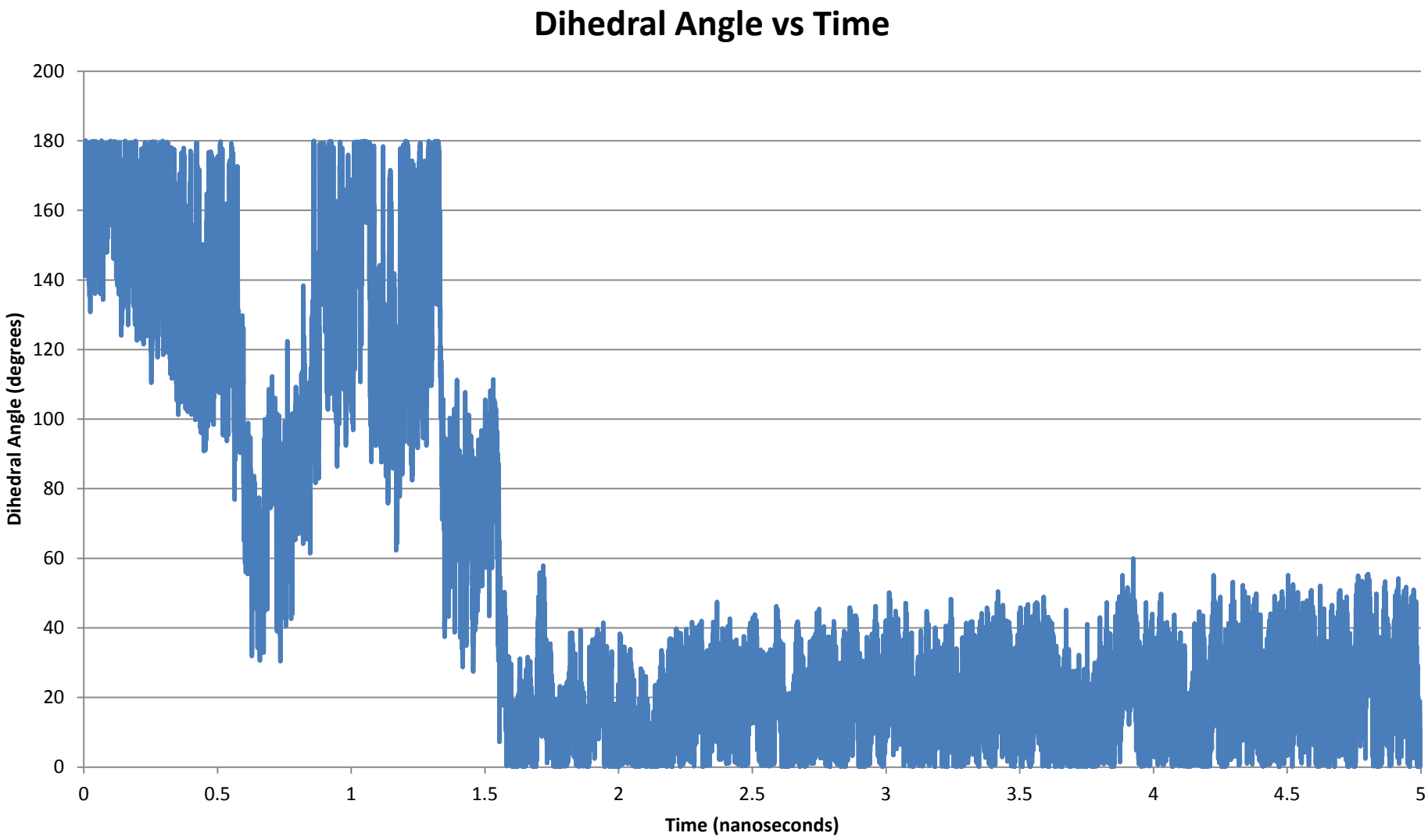
DAP 2A (ABF)


Literature value
energy: ≤9.1 kcal/mol
kcal/mol
0
2
4
6
8
10
12
0
20
40
60
80
100
120
140
160
180
Dihedral Angle (degrees)

DAP 2B (ABF)


16
14
12
10
8
6
4
2
0
kcal/mol
0
30
60
90
120
150
180
Dihedral Angle (degrees)
Literature value energy:
13.6 kcal/mol

Sampling


Dihedral Angle vs Time
Dihedral Angle (degrees)
200
180
160
140
120
100
80
60
40
20
0
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
Time (nanoseconds)

Future Direction

- Run ABF with a distance variable added.
  - Way of measuring energy involved in shuttling.
- Apply bias to allow thread to shuttle through macrocycle.

(Martinez-Cuezva, et al. *Chem. Sci.*, 2015, **6**, 3087-3094)

Acknowledgements

Concordia University
Summer Undergraduate Research Institute

Dr. Andrew Johnson

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