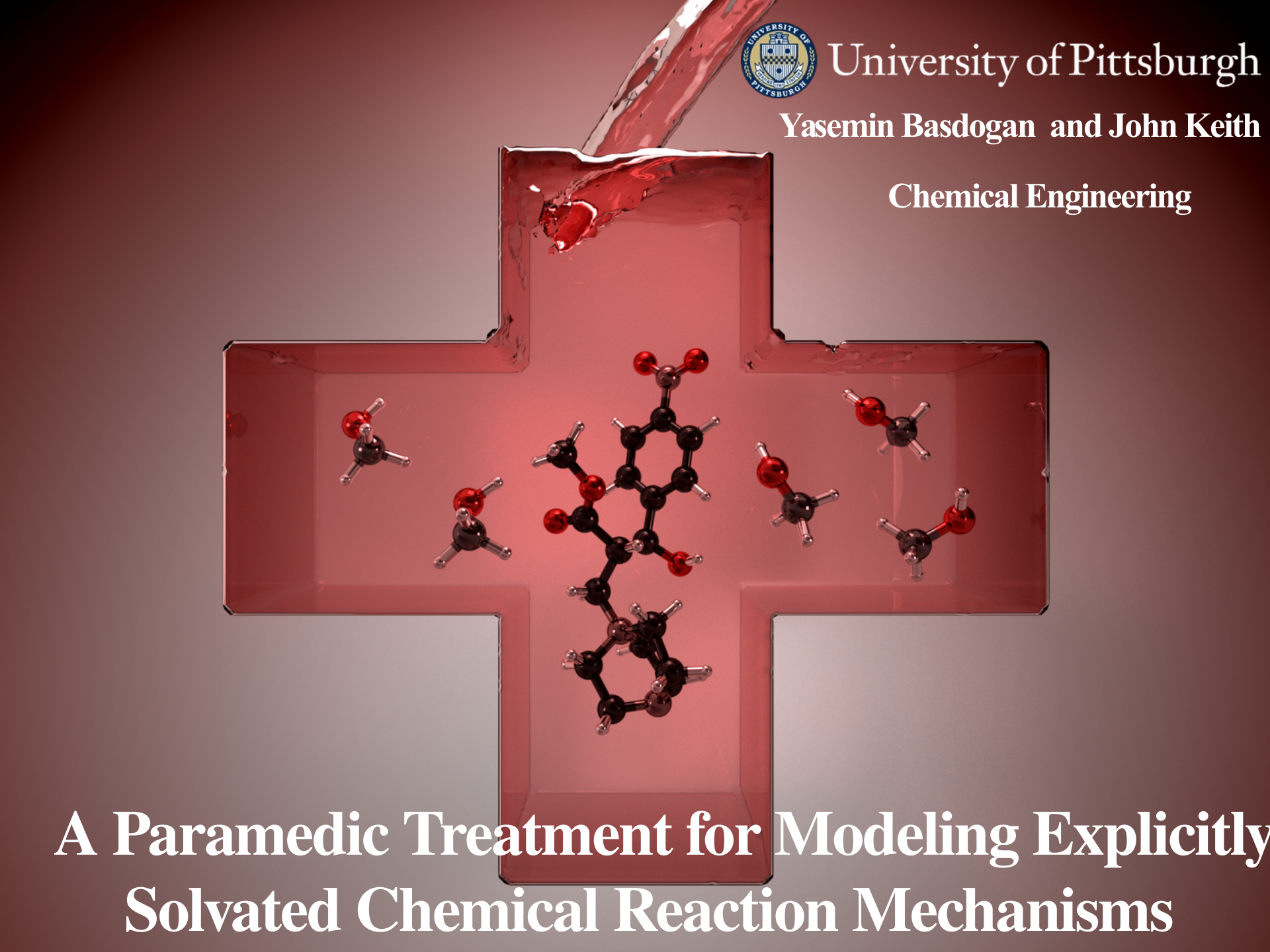


University of Pittsburgh

Yasemin Basdogan and John Keith

Chemical Engineering

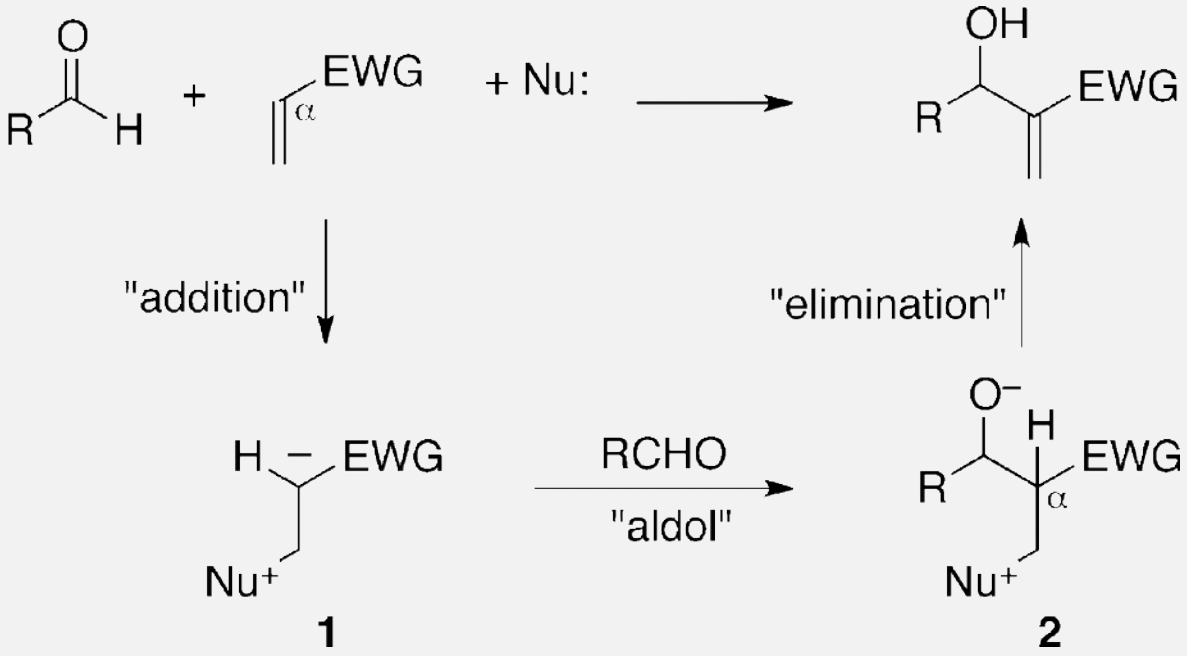
A Paramedic Treatment for Modeling Explicitly Solvated Chemical Reaction Mechanisms

What does Paramedic Mean?

- Easy
- Fast
- Efficient
- Not perfect
- Does not work for all cases
- When it works, it works

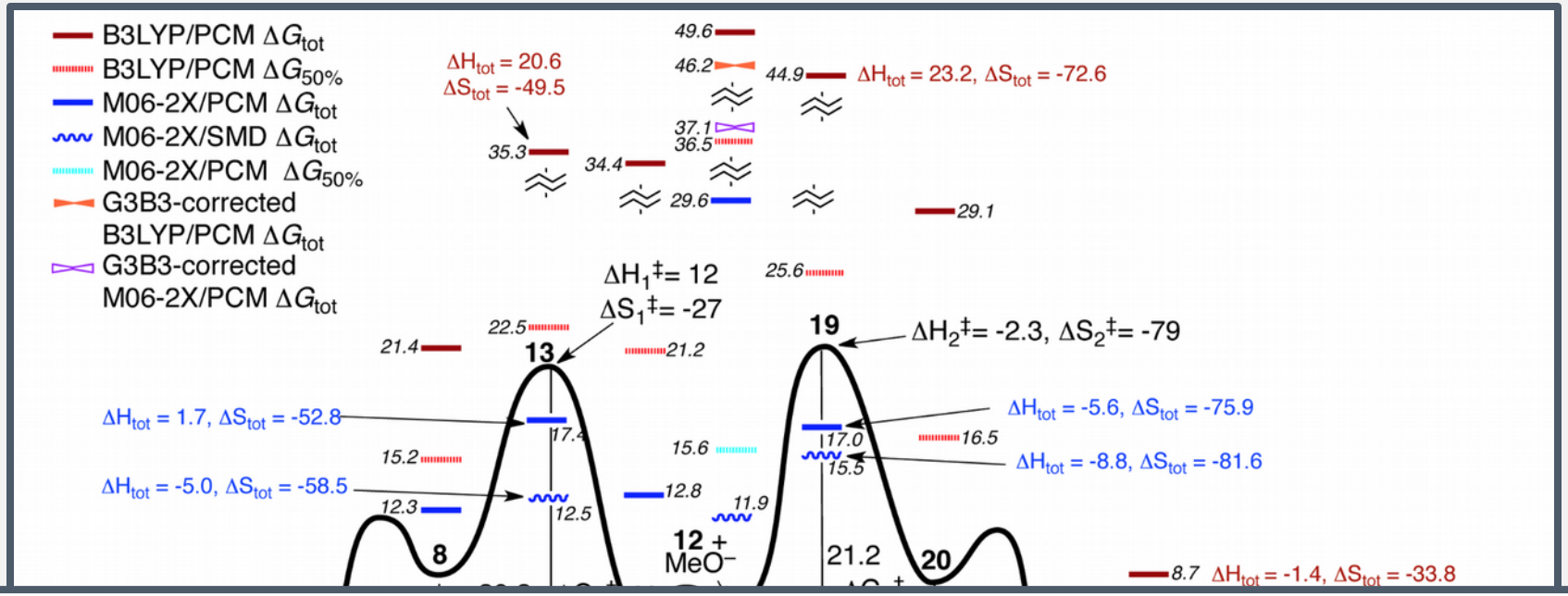
Introduction

- The Morita Baylis Hillman (MBH):
  - Wide range of reactants and products
  - Does not generate waste or byproducts.
- Carbon-carbon bond forming reaction between the α-position of an activated alkene and an aldehyde.



- Wei, Yin, and Min Shi. "Recent advances in organocatalytic asymmetric morita–baylis–hillman/aza-morita–baylis–hillman reactions." *Chemical reviews* 113.8 (2013): 6659-6690.

Literature



So Bad They're 'Not Even Wrong'

STU BORMAN

Chem. Eng. News, **2015**, *93* (10), p 9
DOI: 10.1021/cen-09310-notw8
Publication Date: March 09, 2015

c&en ARCHIVES

Wolfgang Pauli

Nobel Prize in Physics (1945)

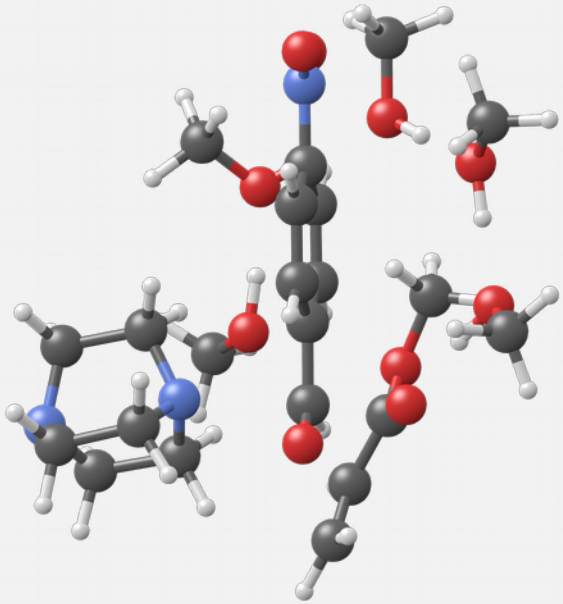
- Plata, R. Erik, and Daniel A. Singleton. "A Case Study of the Mechanism of Alcohol-Mediated Morita Baylis–Hillman Reactions. The Importance of Experimental Observations." *Journal of the American Chemical Society* 137.11 (2015): 3811-3826.

What could be wrong ?

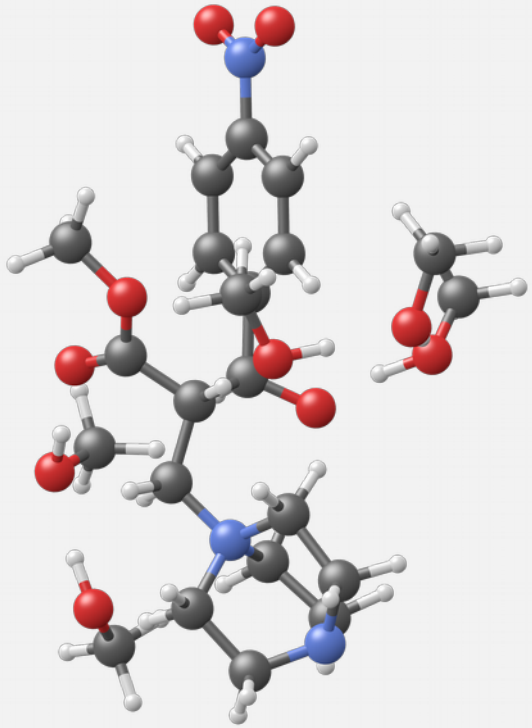
- There could be number of things going wrong from a theorists perspective:
  - Different functionals may be failing.
  - Calculated electronic energies might not be a good representation of experimentally observed Gibbs free energies.
  - Standard solvation approach may fail to capture the solvation effects.
- When someone uses suitable standard approach they fail to capture the important solvation effects.

Hypothesis

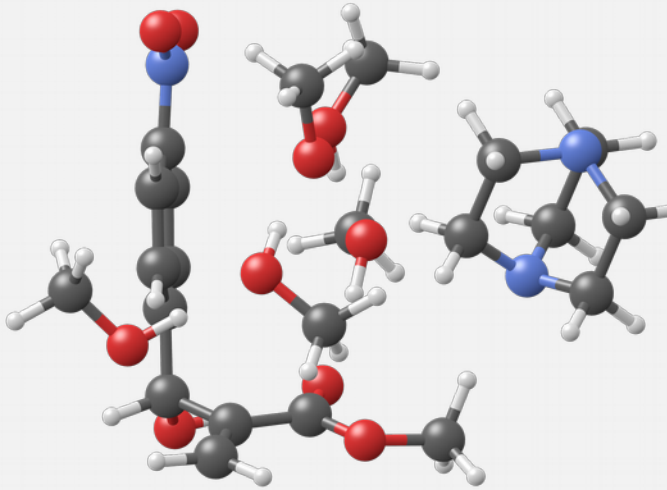
- We believe that incorporating explicit solvent molecules into the calculation will capture critical solvent-solute interactions that are not correctly captured by continuum solvation alone.



Reactants



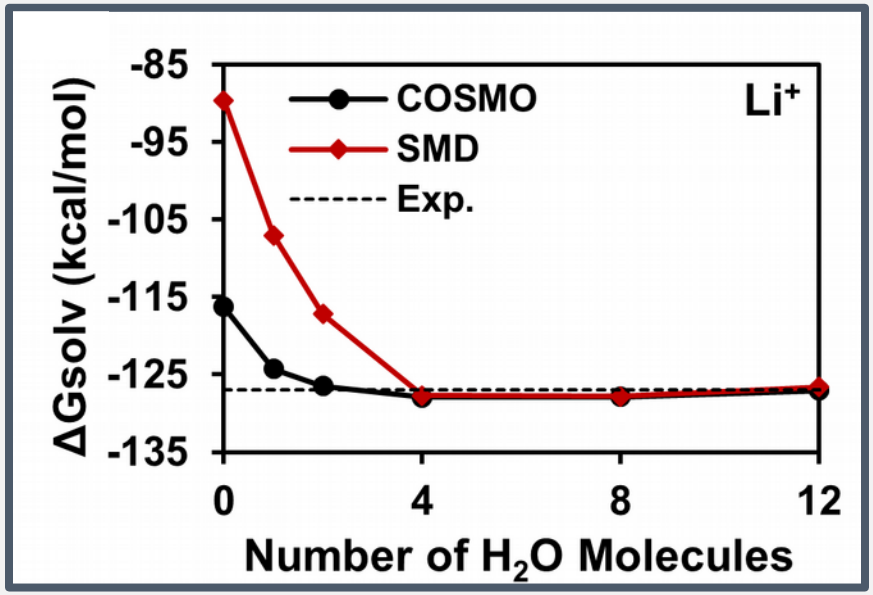
Intermediate 3



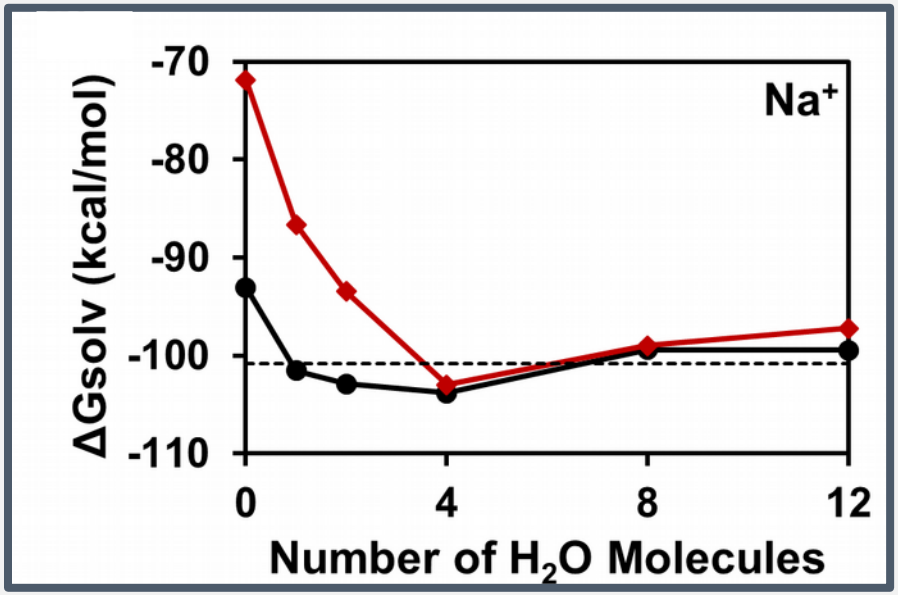
Products

Cluster Continuum Solvation

Li^+ Solvation Energy



Na^+ Solvation Energy



- Solvation energies converge when we include more solvent molecules.

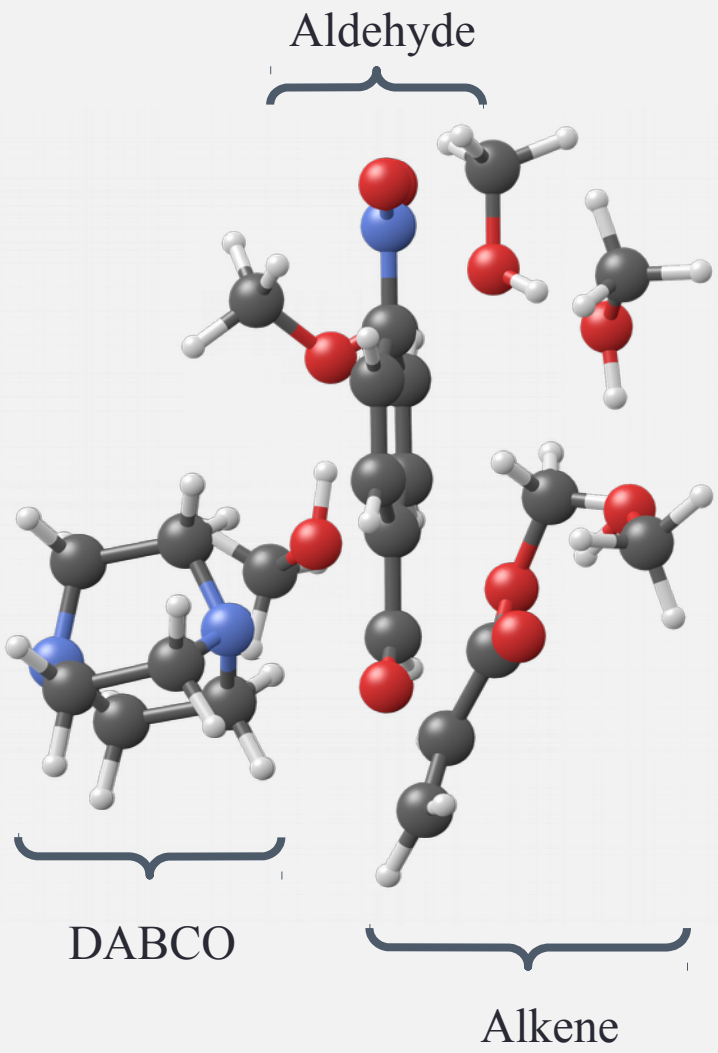
Computational Methodology

ABCluster with a Force Field
(1000 Structures)

MOPAC with PM7
(100 Structures)

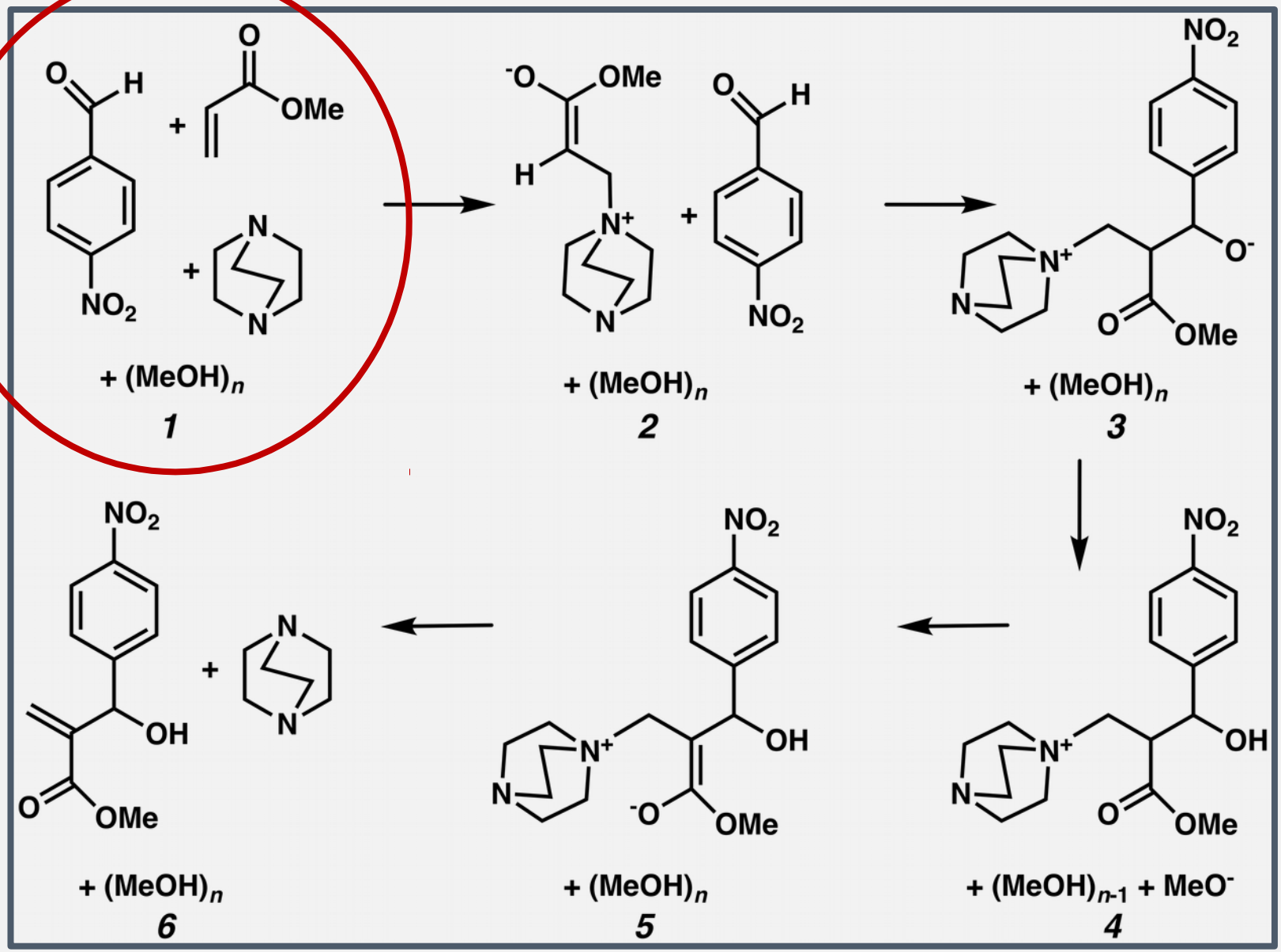
QM Optimization
- BP86-SVP-GasPhase Optimization on PM7 Geometries

QM Single Point
- 4 Different Levels of Theory
- 2 Different Default Basis Set

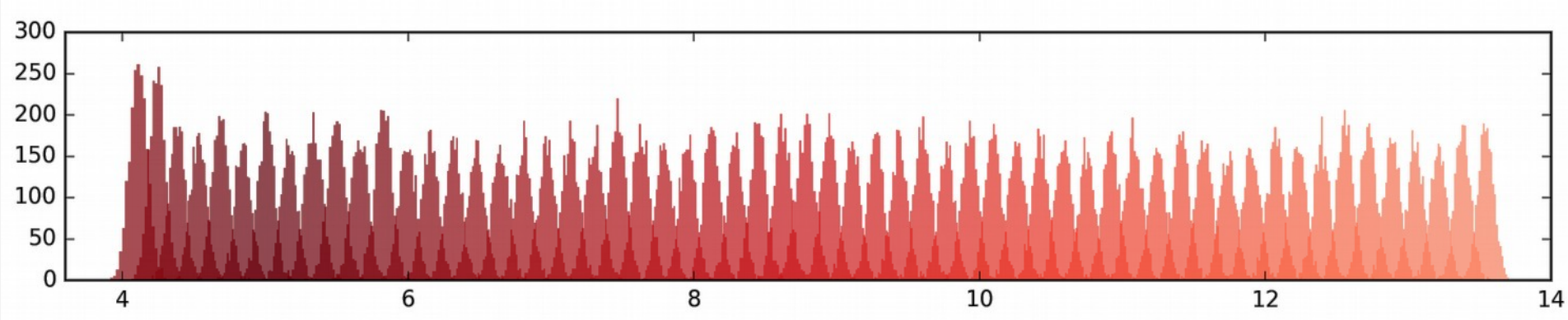


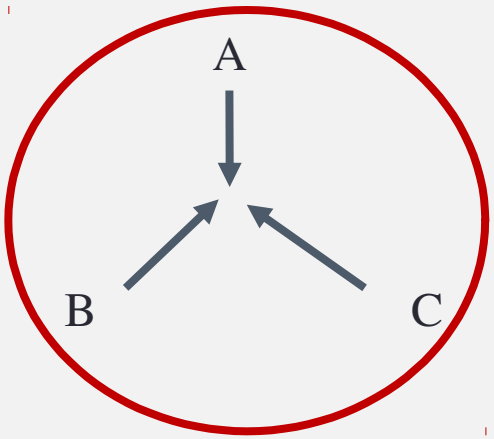
Zhang, Jun, and Michael Dolg. "ABCluster: the artificial bee colony algorithm for cluster global optimization." *Physical Chemistry Chemical Physics* 17.37 (2015): 24173-24181.

Reaction Mechanism

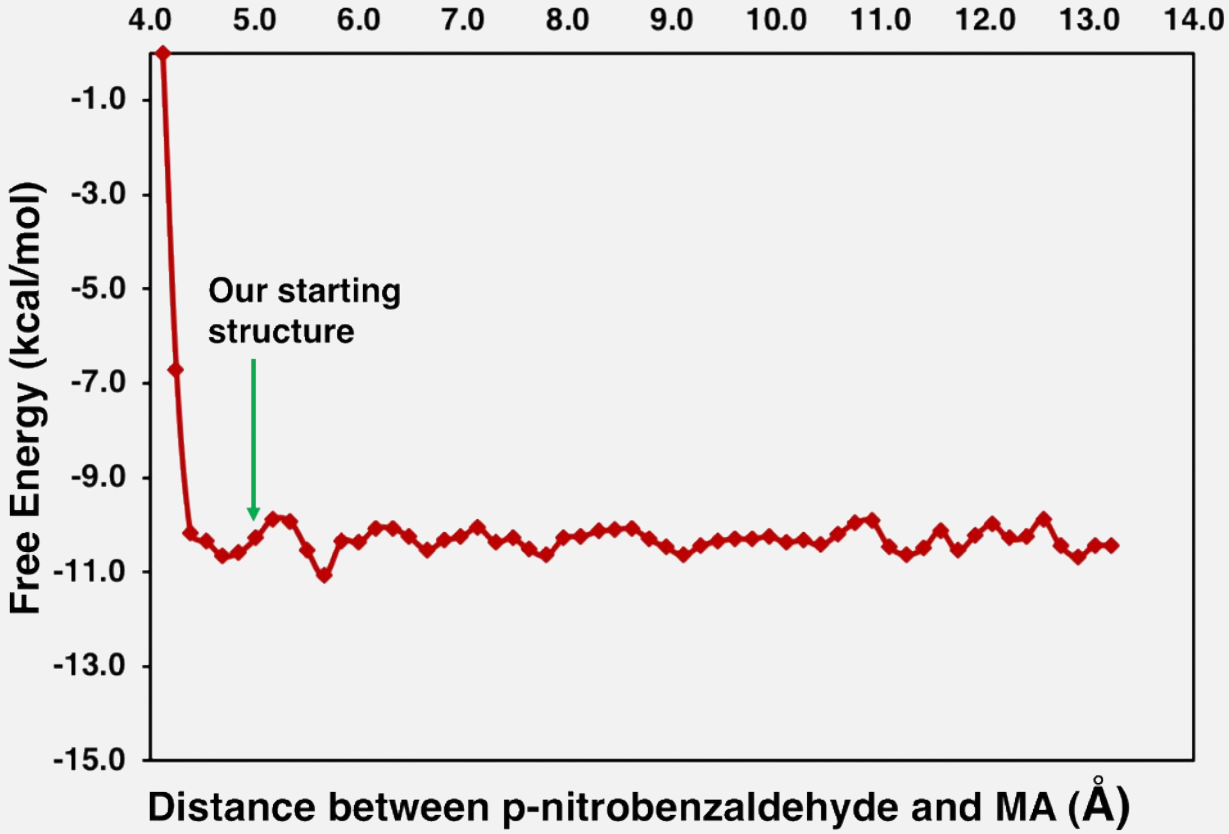


Umbrella Sampling

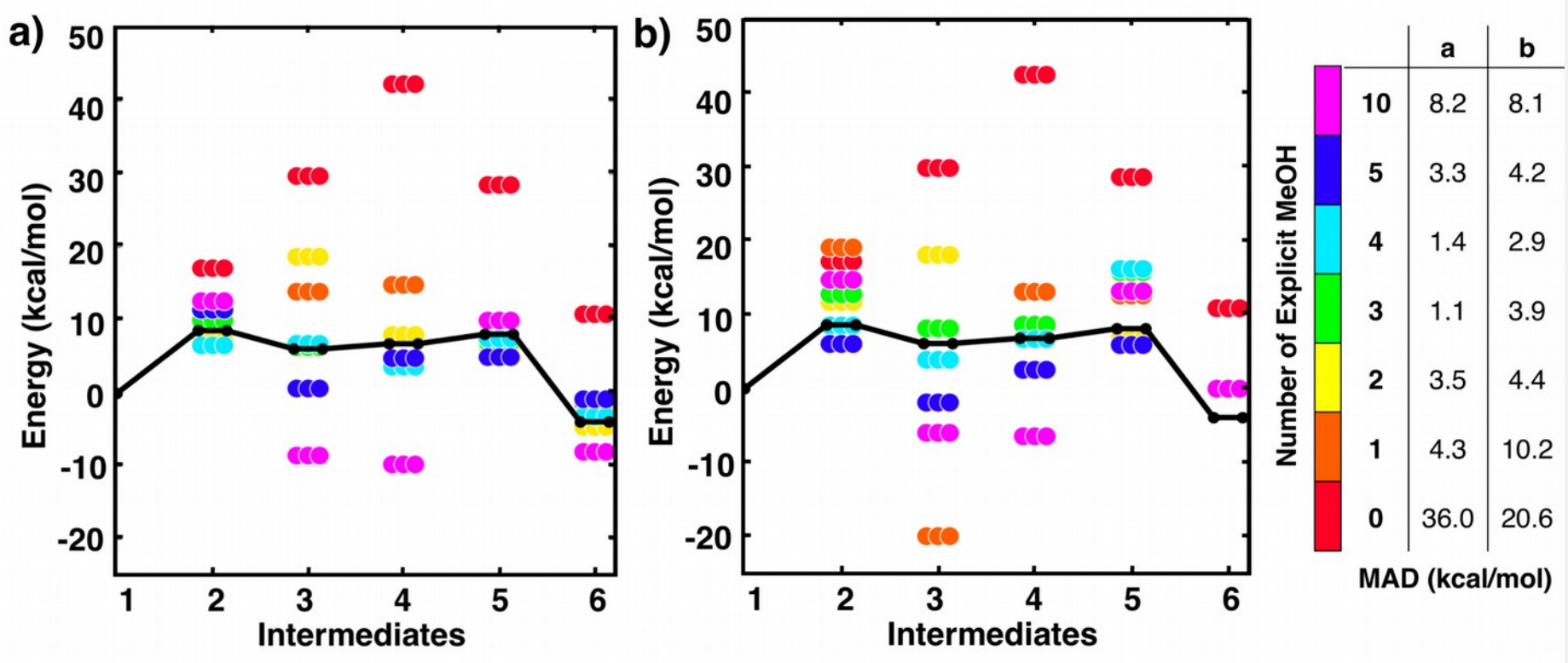




- What is the energy penalty to cluster reactants?

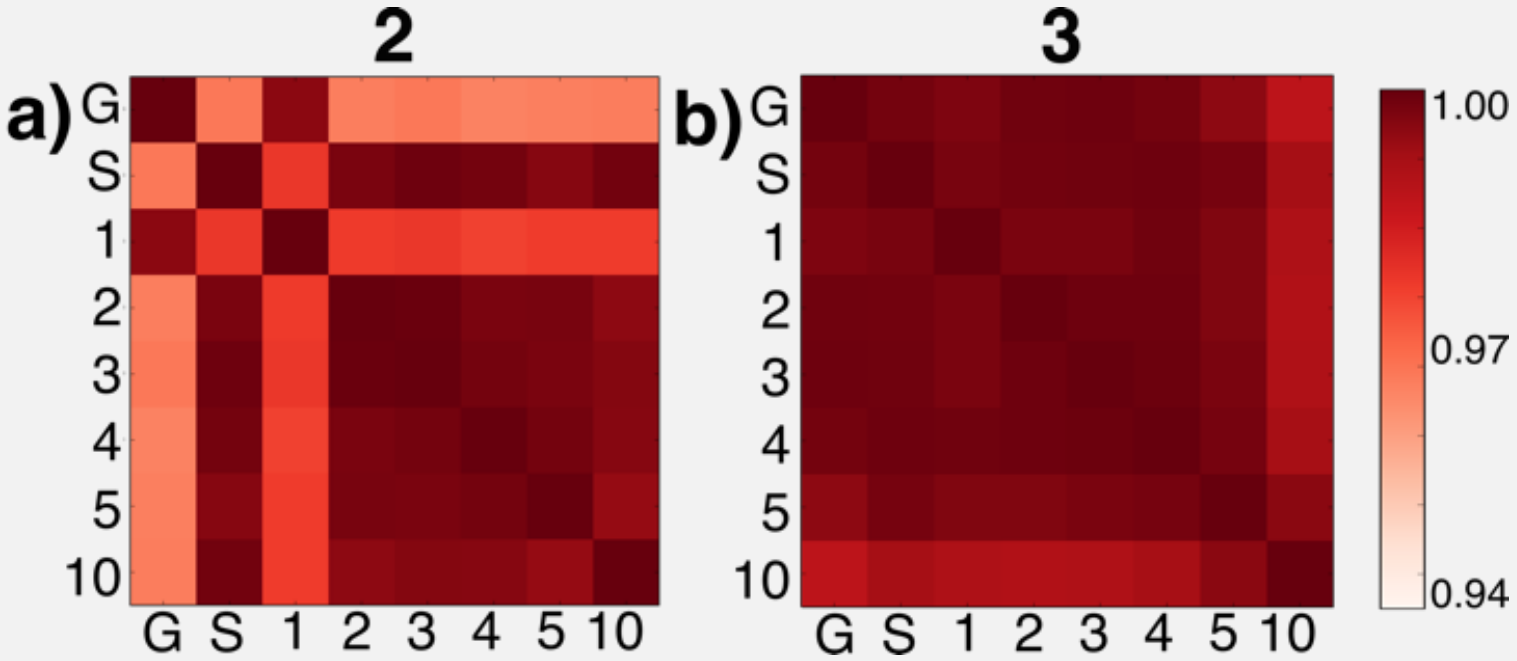


Energy Profile with Static Quantum Chemistry



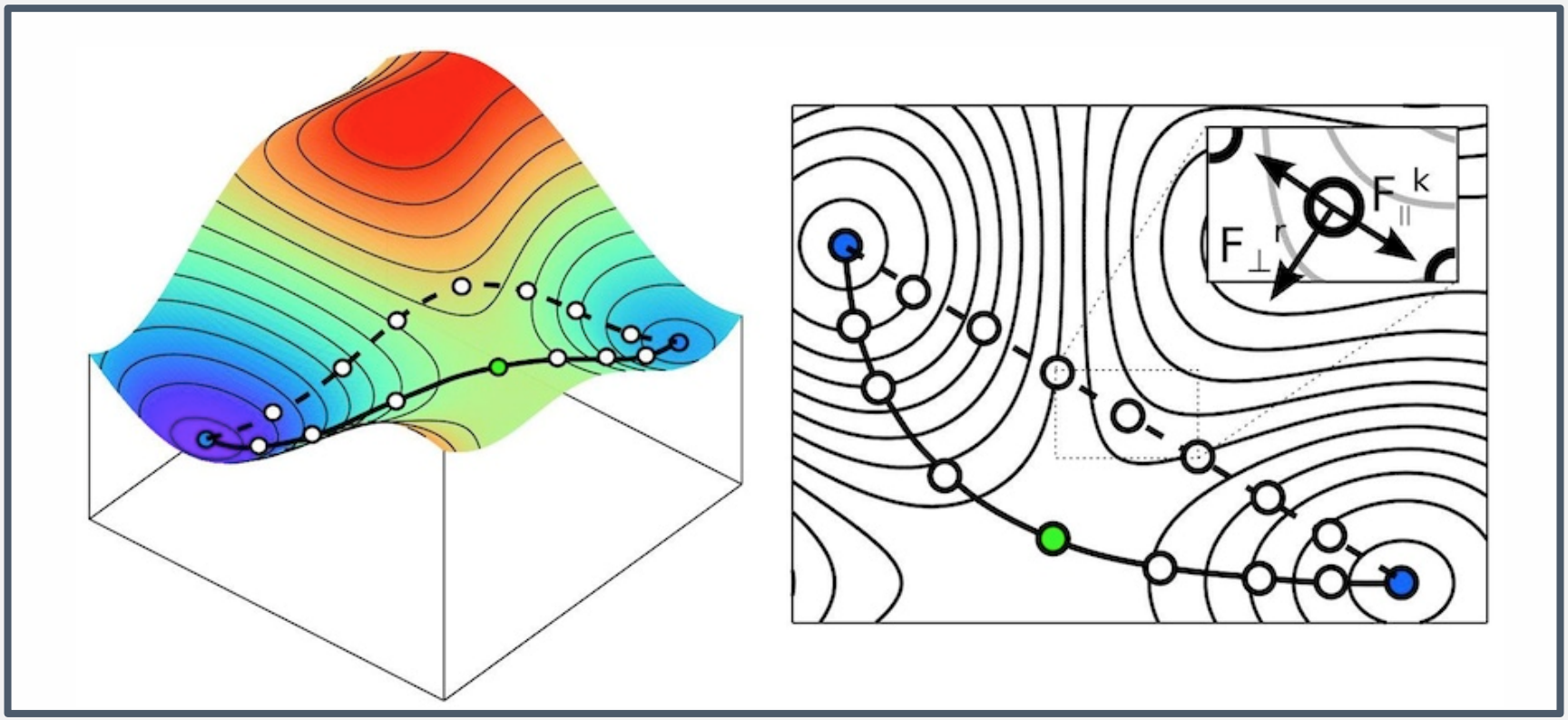
- Gradually adding more solvent molecules into the system does not decrease the errors in energies.
- Continuum solvation models generally did not lower mean absolute deviation (MAD) to experimental data in any case compared to their respective gas phase calculations

ReMatch-SOAP Analysis



- The SOAP analysis of different structures for 2 and 3 shows very high geometric similarities for all solute structures when optimizations were run with two or more explicit methanol molecules.
- This shows that the 10 – 30 kcal/mol scatter in energies for each intermediate shown on precious slide is due to modeling errors in solvation energy contributions.

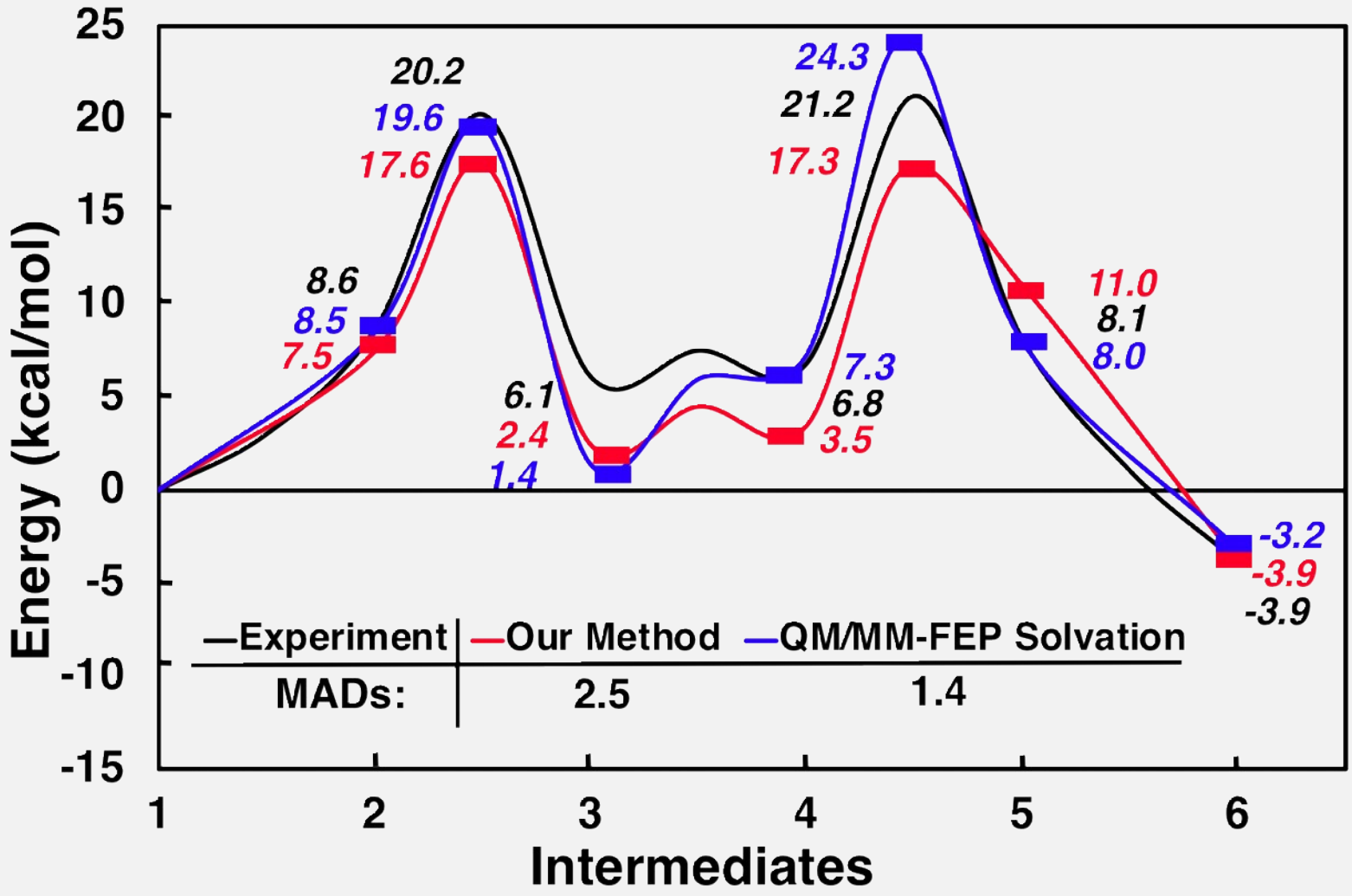
Growing String Method (GSM)



- Highly useful for locating reaction paths connecting two molecular intermediates.
- Procedure to locate exact transition states.

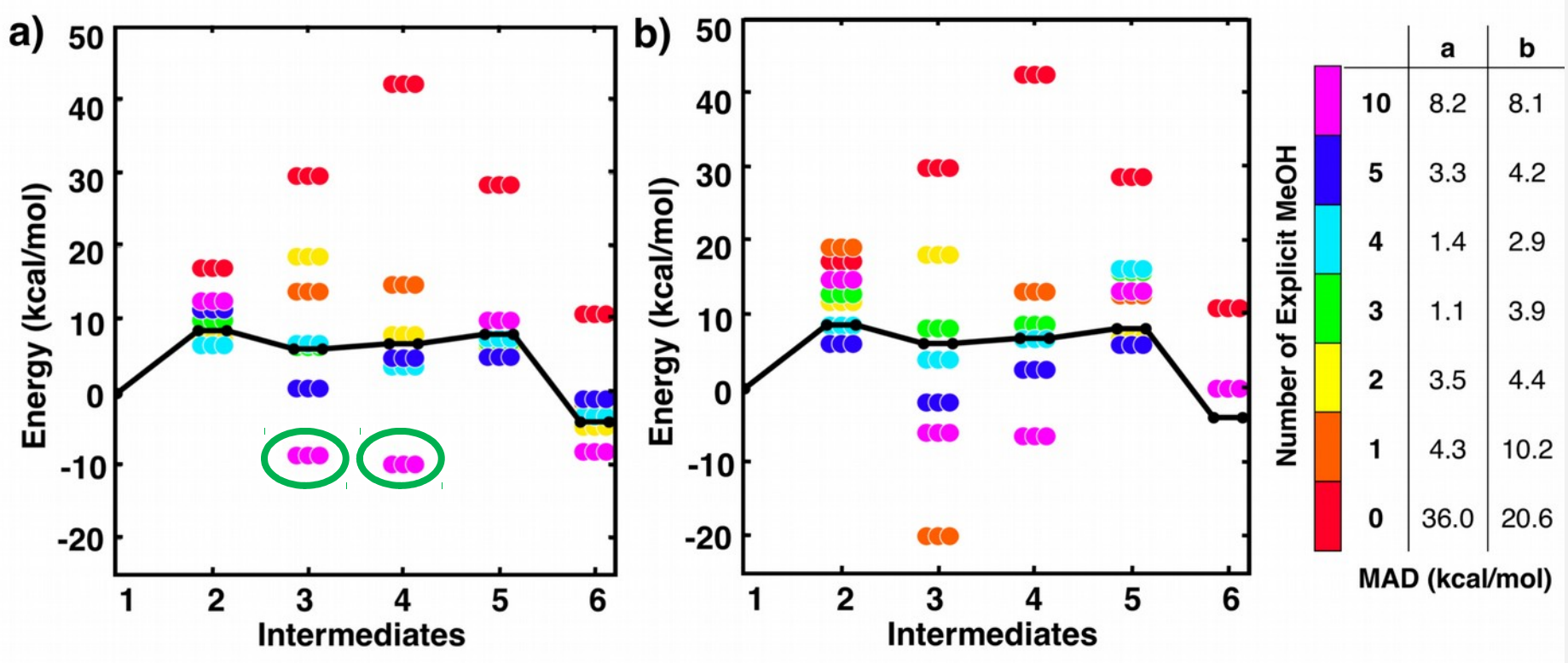
Zimmerman, Paul M. "Growing string method with interpolation and optimization in internal coordinates: Method and examples." *The Journal of chemical physics* 138.18 (2013): 184102.

Overall Energy Profile with GSM



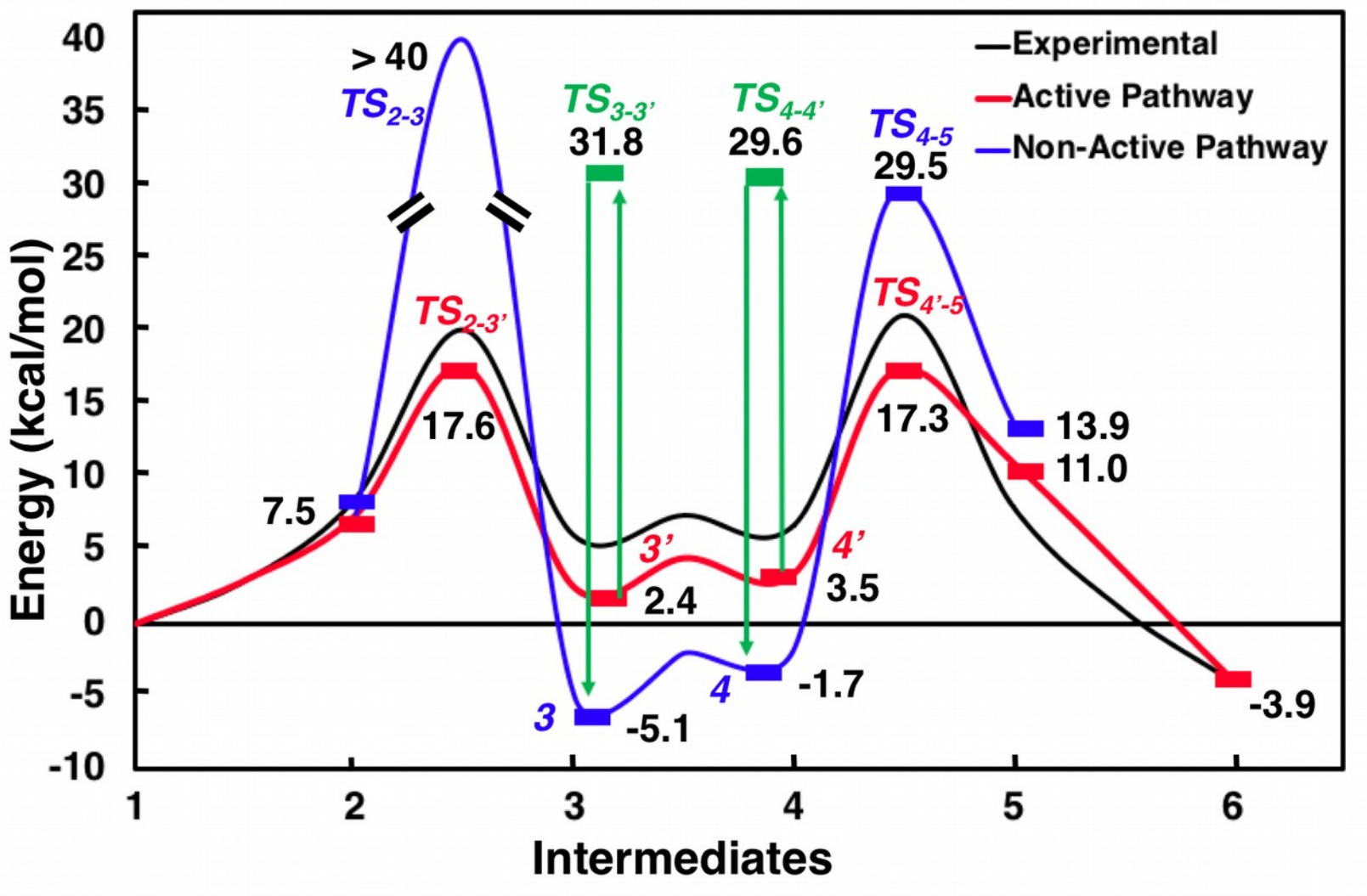
❖ Our modeling scheme identifies a complicated reaction mechanism with comparable accuracy as models using computationally demanding explicit solvation methods.

What happened to the initial data?



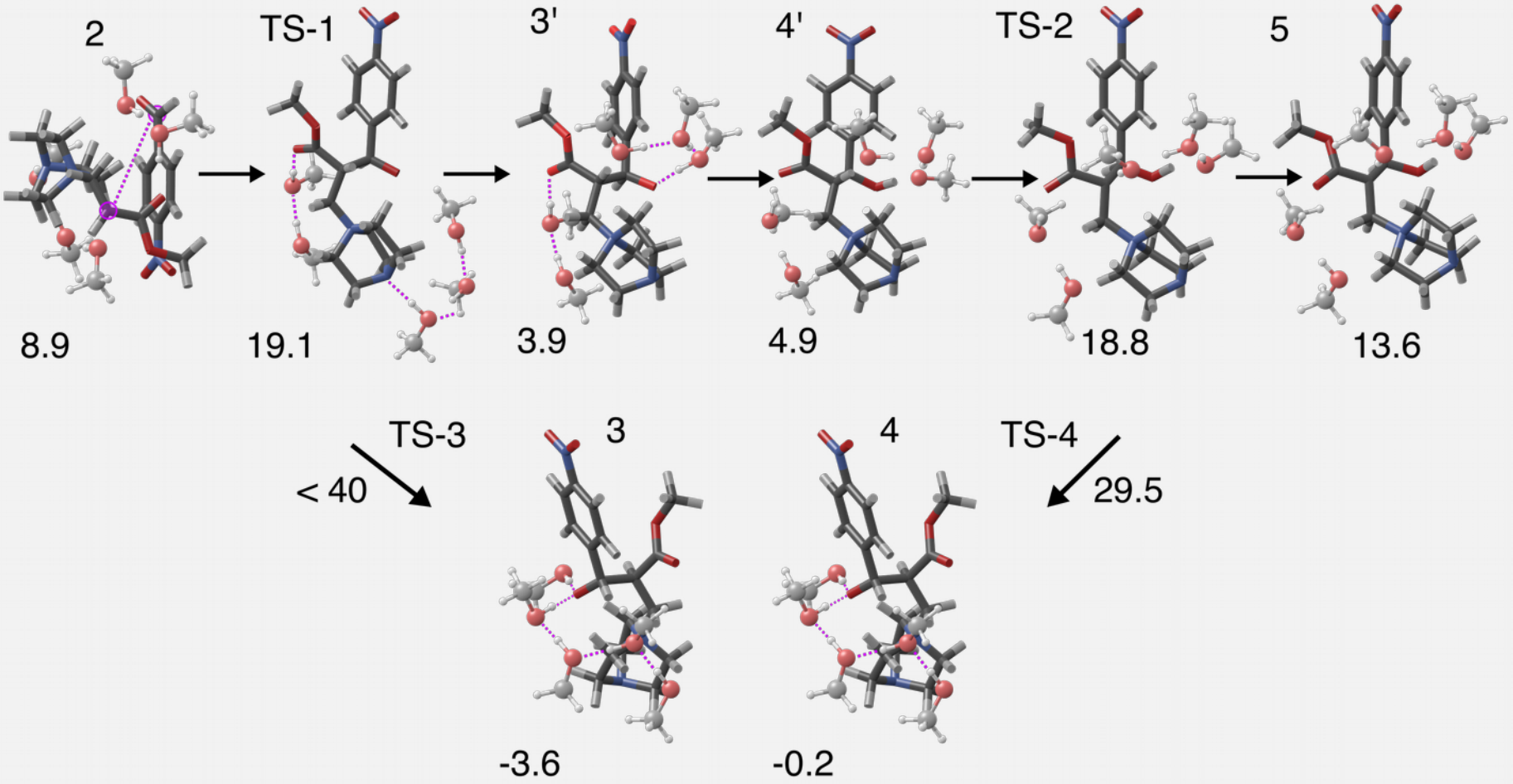
- Why does QM results with these unrealistically stable structures?

Double Ended GSM



❖ This means that the MBH reaction occurs with pathways that are not along minimum energy intermediates.

Structures



- The local solvent environment around a solute plays a critical role in stabilizing reaction intermediates.

Summary

- **Step 1:** Identify globally optimized clustered states for hypothetical reactant states with different numbers of solvent molecules.
- **Step 2:** Perform umbrella sampling simulations using explicit solvent models to show these are adequate representations of reactant states.
- **Step 3:** Calculate energies and do Rematch-SOAP analysis to see if your energies or geometries are converging.
- **Step 4:** Systematically explore reaction pathways using single-ended GSM calculations and eliminate models that give unrealistic barriers

- When successful, this paramedic treatment should be a robust and automatable way to model other challenging reaction mechanisms that involve explicit solvent molecules.

Keith Group

Thank you for listening…