



Computational Examination of Water Adduction to Lithiated Cannabinoids

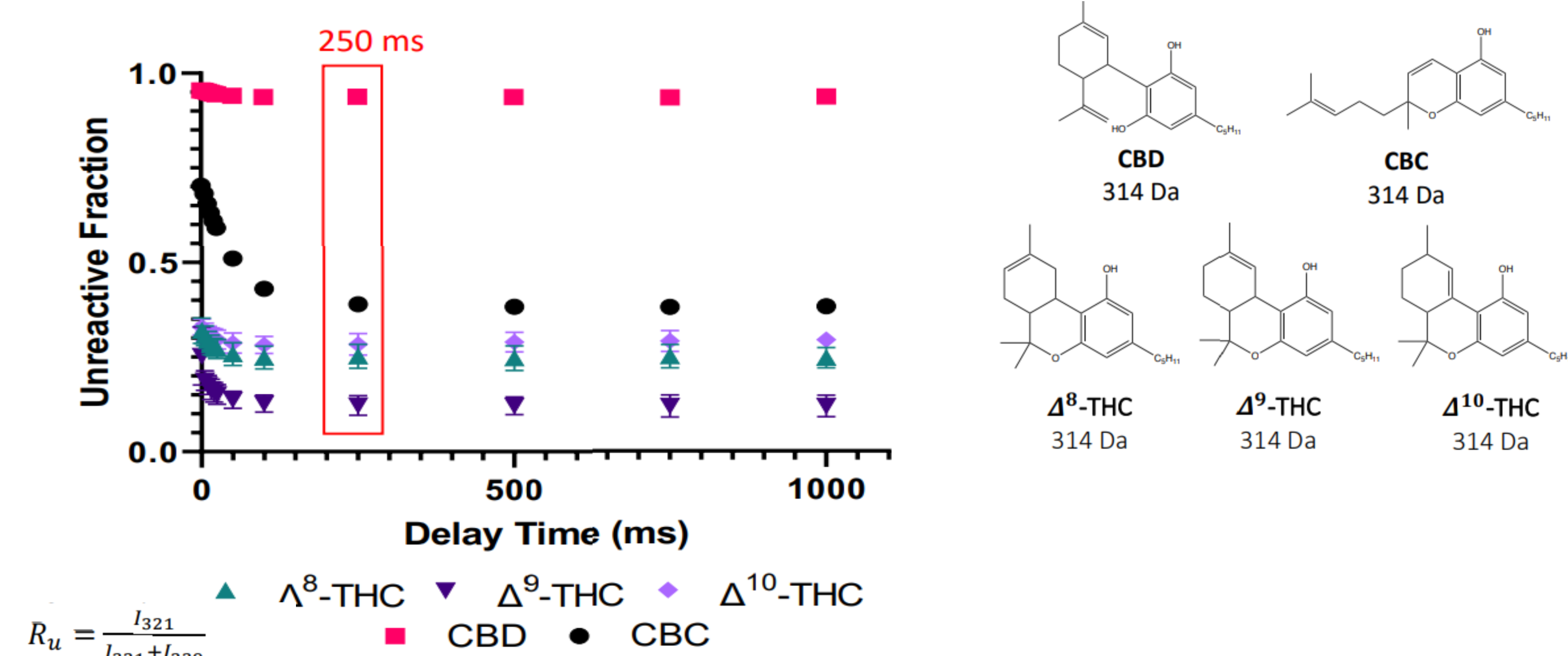
Conner J. Baucom, Gary L. Glish, and Shubin Liu.

Department of Chemistry, The University of North Carolina at Chapel Hill, Chapel Hill, NC

THE UNIVERSITY
of NORTH CAROLINA
at CHAPEL HILL

Introduction

Lithium cationized isomers can often be differentiated by a simple water adduction reaction in quadrupole ion trap mass spectrometry. We have previously used this approach with carbohydrates (pentoses, hexoses and disaccharides). Subsequently we have determined cannabinoid isomers can also be identified via water adduction to the lithium cationized cannabinoids (CBD, various THC isomers). Experimentally, CBD shows very little water adduction while for the THC isomers 60-85% water adductions is observed. The cannabinoids are different than the carbohydrates though because the potential sites of lithiations are much fewer but with greater chemical variety with the possibility of cation-pi interactions. With carbohydrates, DFT calculations suggest that water adduction is observed when lithium is bound in a bidentate interaction, but not for tri or tetra dentate interactions. For the cannabinoids however, there has not yet been a tridentate binding conformation observed for any of the compounds tested. In this work, we use high level double hybrid theory to elucidate the nature of water adduction for lithiated cannabinoids



Computational Methods

Thermochemistry calculation of water adduction:

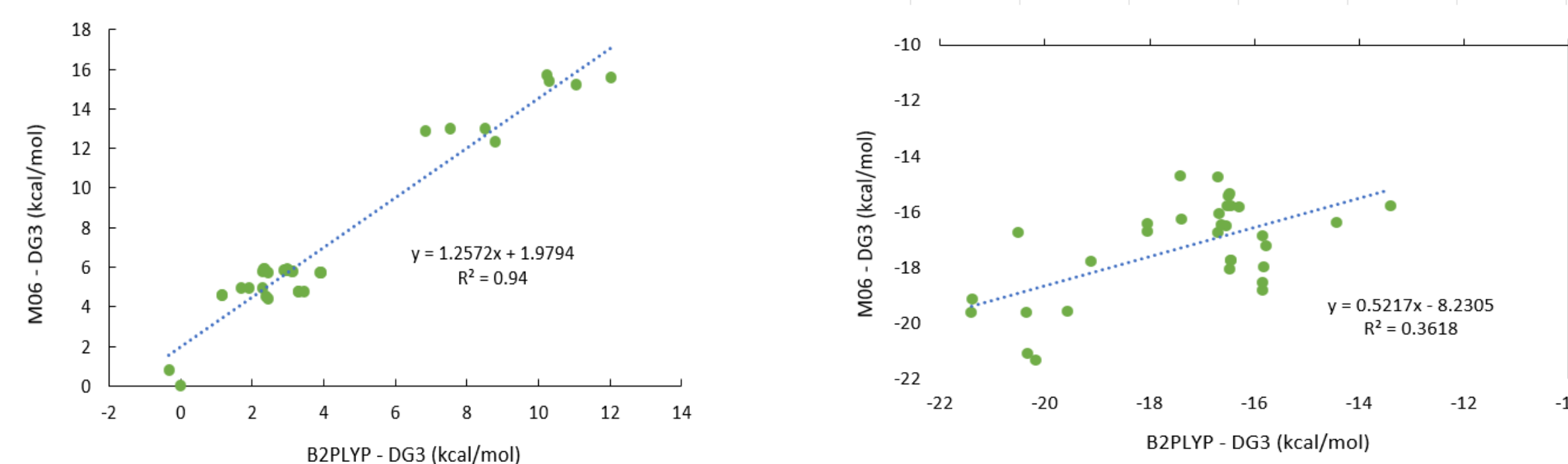
- B2PLYP Double Hybrid Functional with Grimme's GD3 dispersion correction. 6-31G(d) basis set for carbon and hydrogen. 6-311+G(d) basis set for Lithium and oxygen

Solution phase lithiated complex with explicit solvation ligands:

- Same as water adduction calculations with SMD implicit solvation model using methanol as solvent environment
- Explicit water molecules attached to lithium to simulate 95:5 methanol water solution used in experiments. Lowest energy conformation selected for each binding orientation.

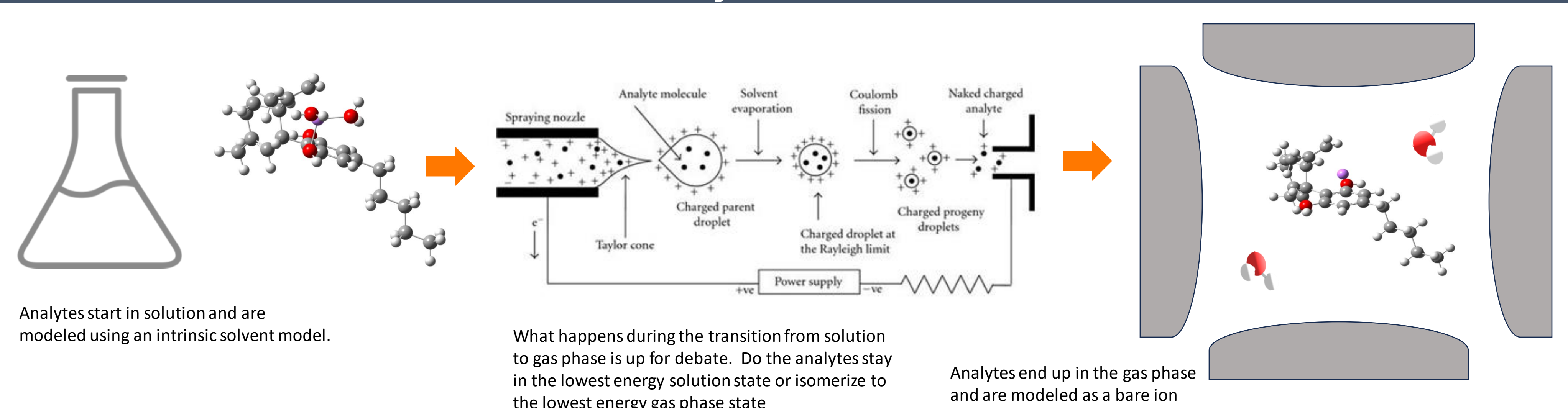
Transition state energies, Intrinsic Reaction Coordinates and Internal bond rotation energy scans use combination of M06-DG3/6-311+G(d) and M062X/6-311+G(d)

- All transition states found with QST3 and verified with subsequent IRC

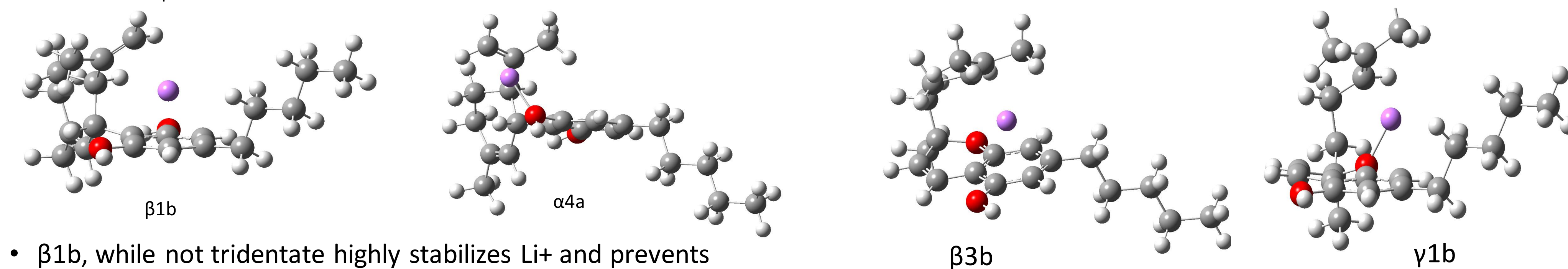
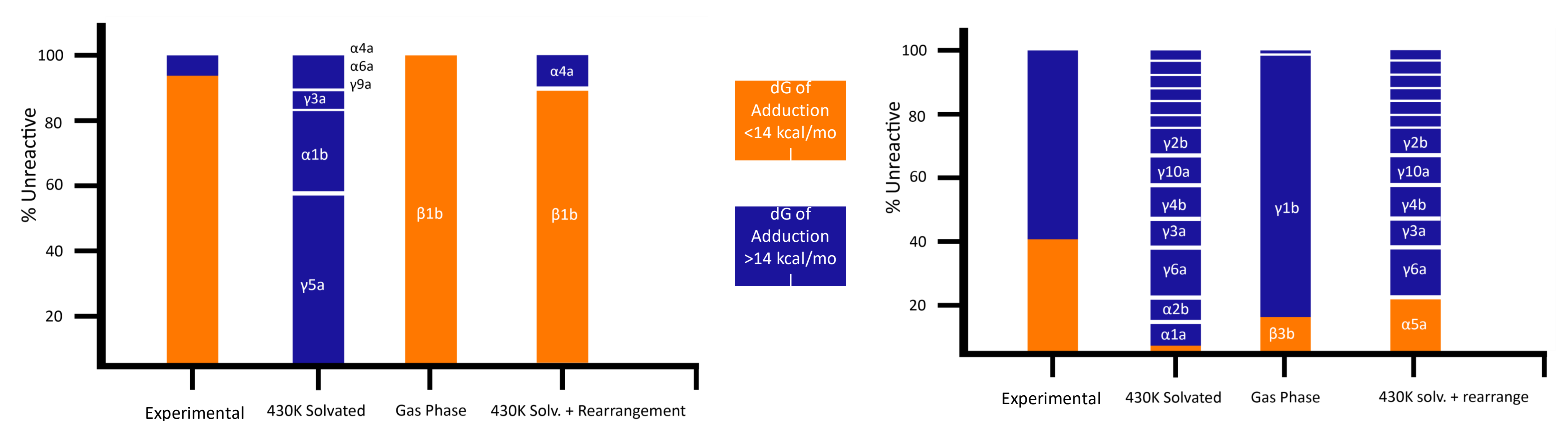


Figures 1 and 2. Agreement for M06 and B2PLYP is much better for lithiated cannabinoid Gibbs free energy than for water adduction free energy.

How should systems be modeled?



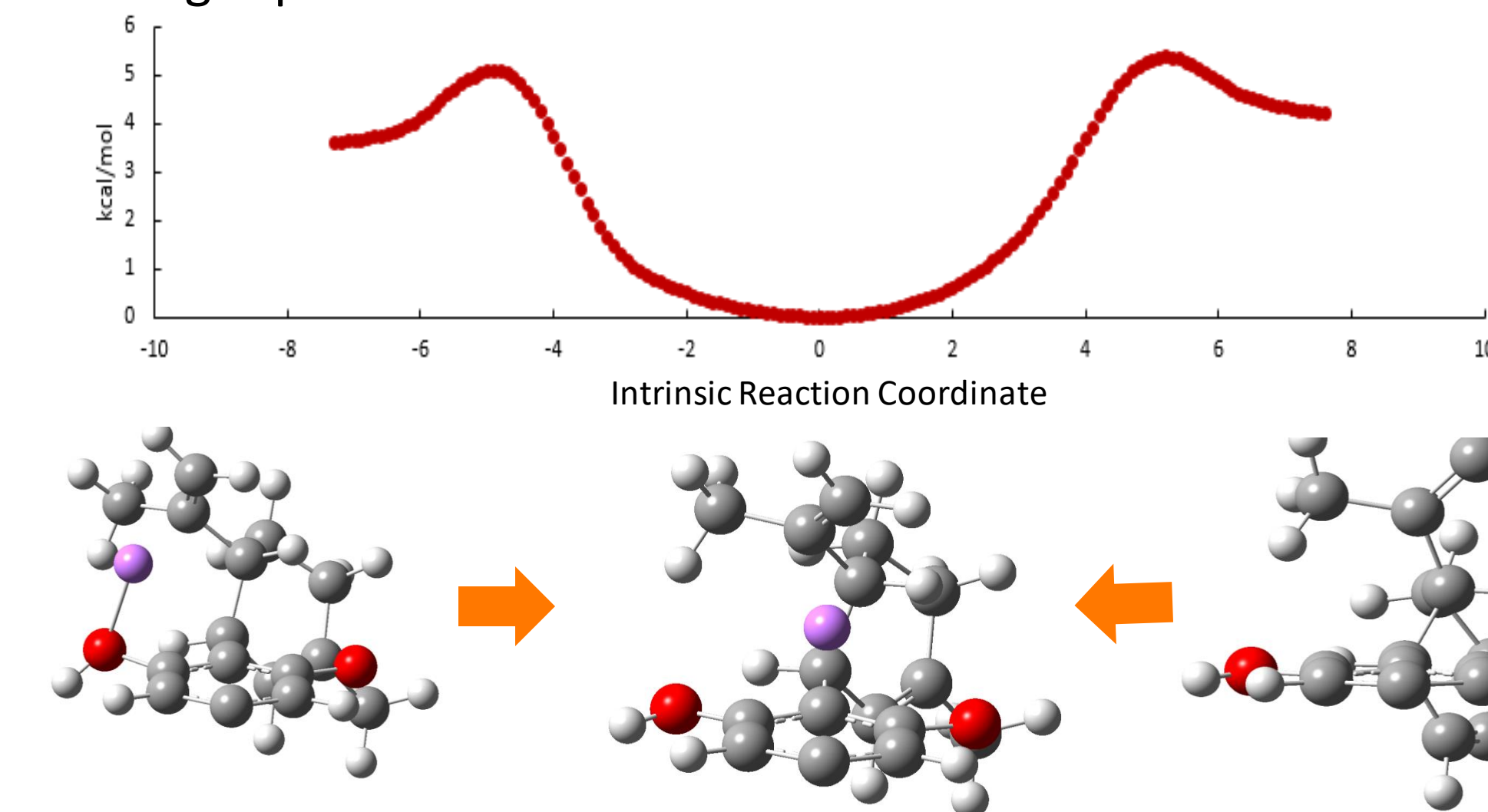
Cannabidiol (CBD) and Cannabichromene (CBC)



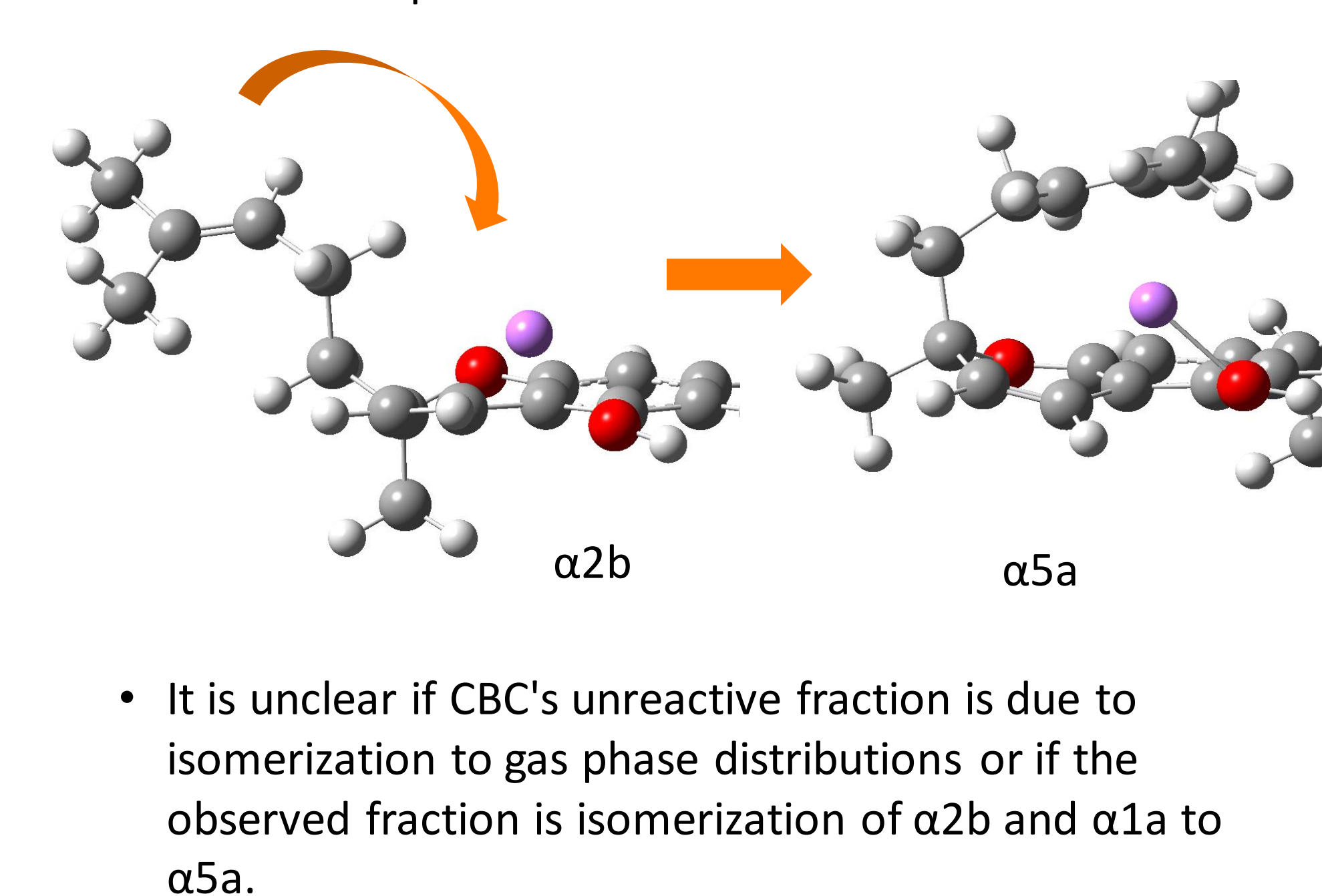
- beta1b, while not tridentate highly stabilizes Li+ and prevents water adduction
- alpha4a propenyl group has high rotational energy barrier (~7 kcal/mol), likely kinetically trapping Li+, allowing observed minute water adduction.

Reisomerization

- Li+ may transit freely from gamma5a and alpha1b to beta1b as shown on the intrinsic reaction coordinate below. Thus, CBD spontaneously isomerizes to an unreactive form when entering the gas phase.



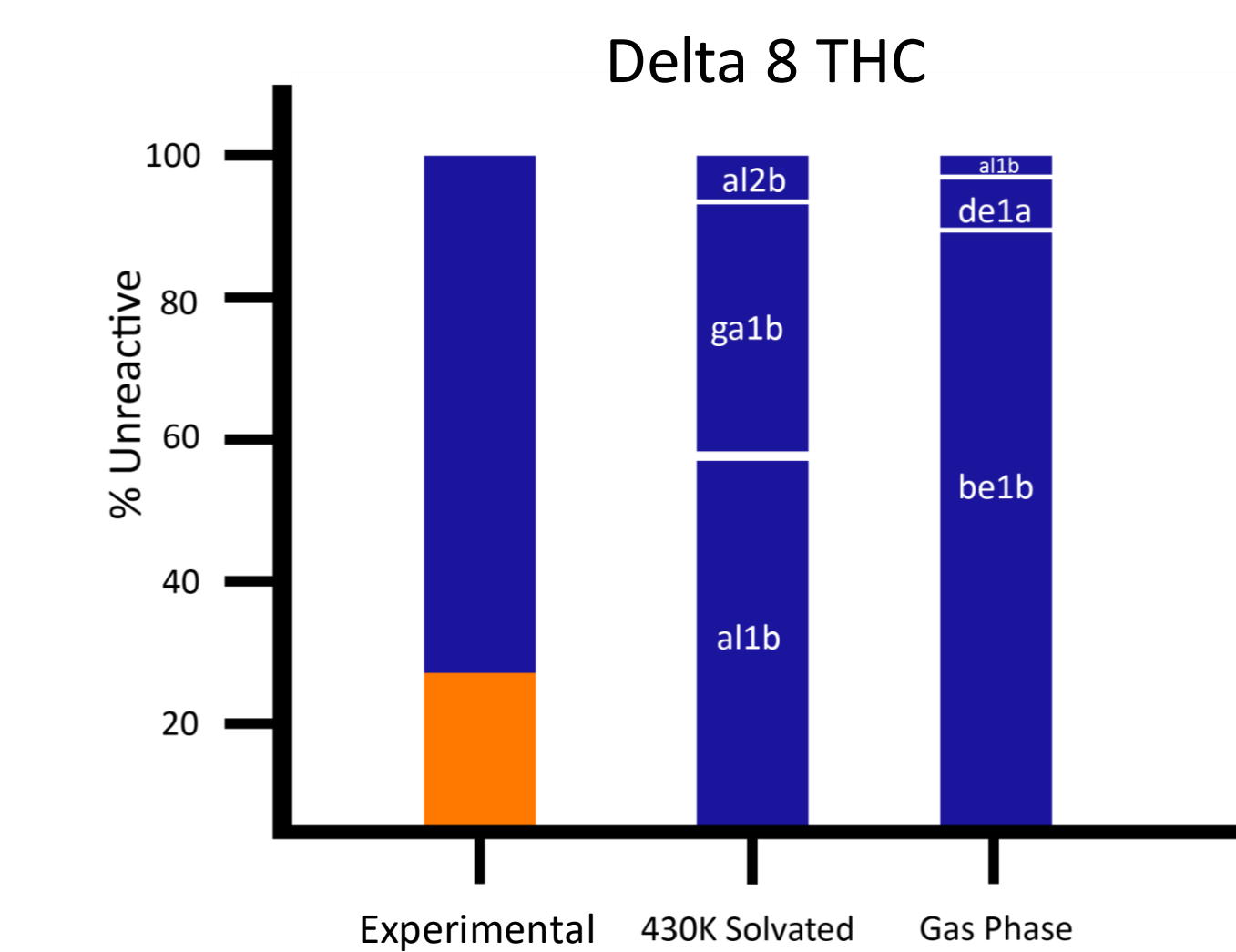
- Internal bond scans show alkene tail of CBC is highly mobile (barrier of < 2 kcal/mol). For alpha structures, it is likely the tail clamps onto Li+, producing alpha5a, an unreactive species.



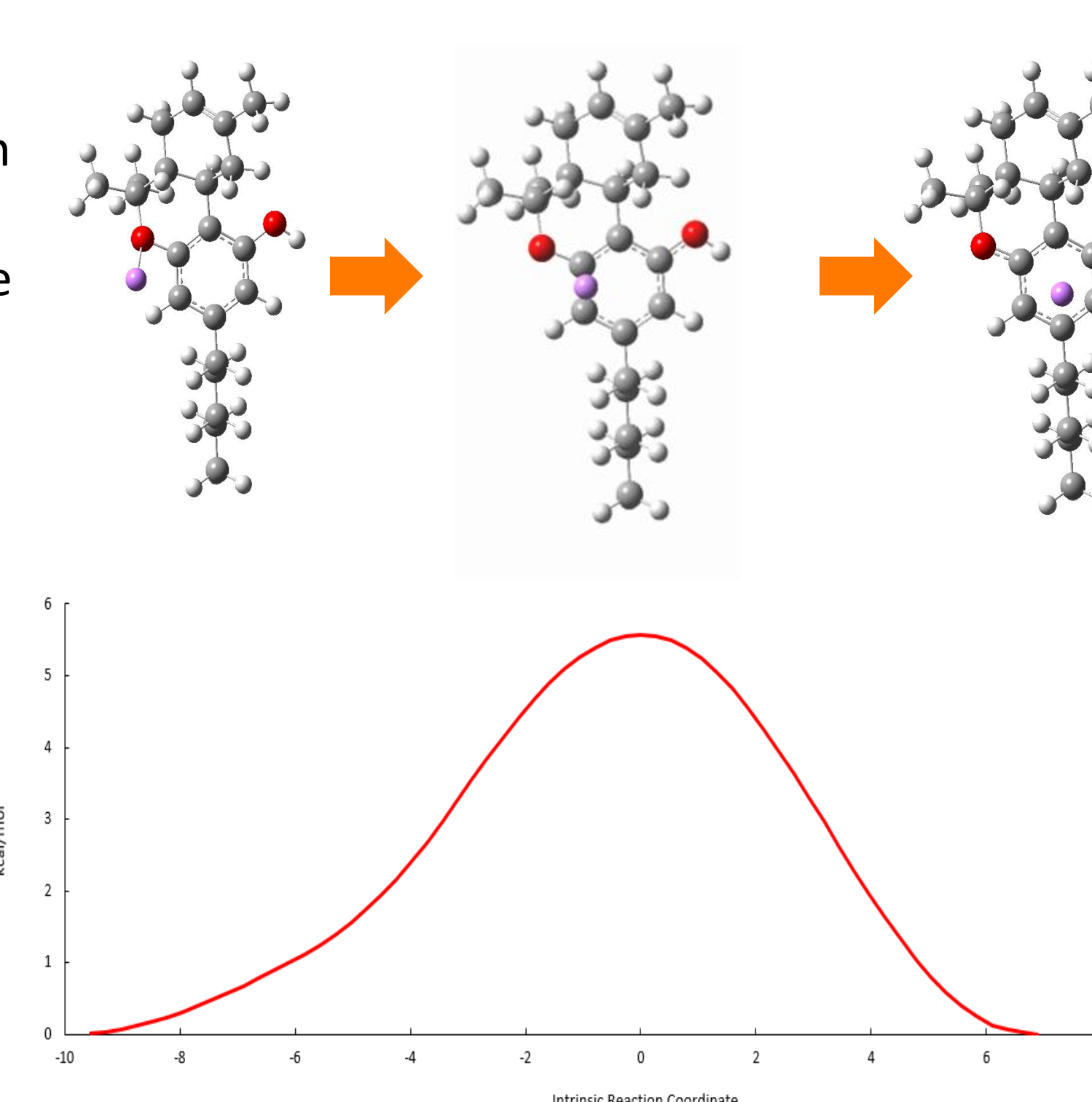
- It is unclear if CBC's unreactive fraction is due to isomerization to gas phase distributions or if the observed fraction is isomerization of alpha2b and alpha1a to alpha5a.

Delta Tetrahydrocannabinol(s)

- So far, no unreactive binding sites have been found for Delta 8, Delta 9 or Delta 10 THC. We have hypothesized a possible ring opening mechanism to form a CBD like structure; however, the energies seem too high for the environment.



- Similarly to CBD, cation transit isomerization pathways have been mapped for Delta 8 THC. It is unclear whether the activation energy barrier (~5 kcal/mol) is reasonable to be observed in the reaction conditions.



Conclusions

- Several DFT functionals have been shown to be inadequate to model water adduction energies for metal cations. Higher level theories are likely necessary.
- Lithium cations will transit from phenol oxygens to their benzene and back in the gas phase with sufficient energy.
- With **currently available conformers**, water adduction to CBD seems to be well described by the solvated complex distribution at 430 K.
- While no unreactive binding sites have been found for the THC cannabinoid isomers, experiments and computation are ongoing to elucidate their puzzling nature.

References

Fernando, D.; Worthington, C.; Glish, G. Using Water Adduction to Differentiate Cannabinoid Isomers in a Quadrupole Ion Trap Mass Spectrometer. 2023 Celebration of Undergraduate Research Symposium, UNC Chapel Hill, 2023.

Banerjee, Shibdas & Mazumdar, Shyamalava. (2012). Electrospray Ionization Mass Spectrometry: A Technique to Access the Information beyond the Molecular Weight of the Analyte. International journal of analytical chemistry. 2012. 282574. 10.1155/2012/282574.

Gaussian 16, Revision C.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2016.