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Background

Acetylated Cannabinoids

- Phytocannabinoids, or **Cannabinoids**, are compounds produced naturally in plants of the *cannabis* genus
- Cannabinoids** have been used in the treatment of glaucoma, epilepsy, and terminal illnesses, one ROA includes **vaping**
- Certain **cannabinoids** are able to **acetylated** through a nucleophilic acyl substitution with acetic anhydride, producing semi synthetic cannabinoids. This poster will be focused on acetylated **delta-8 tetrahydrocannabinol** and **cannabinol**

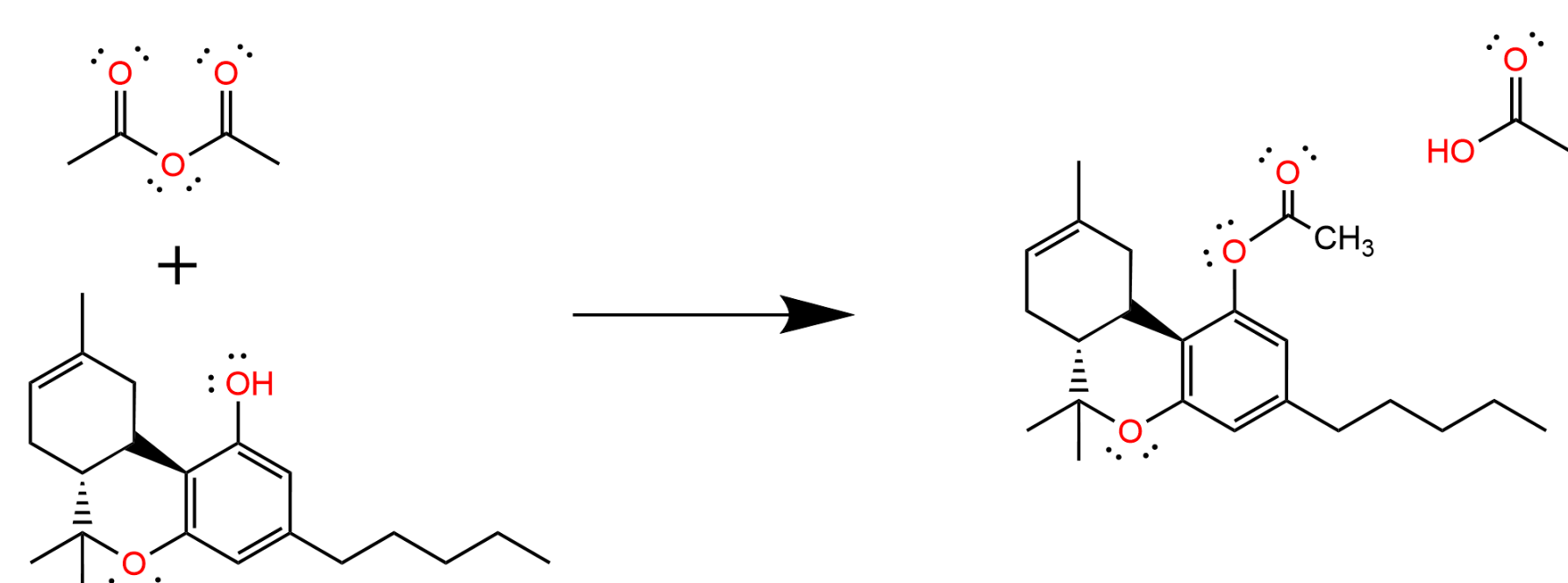


Figure 1. Conversion of delta-8 tetrahydrocannabinol to delta-8 tetrahydrocannabinol acetate with acetic anhydride.

- Acetylated cannabinoids** have increased potency due to **non polar acetyl group** (high blood brain barrier permeability)
- Certain **acetylated cannabinoids** are federally legal and have seen widespread recreational use

Ketene Formation

- Ketene** gas has high pulmonary toxicity and has been demonstrated to be fatal
- As of 2020, there has been ~3,000 lung injury related hospitalizations and deaths attributed to ketene formation from vitamin E found in commercial vaporizers³
- Study in 2022 by Munger et al. detected **ketene** formation upon heating of **acetylated cannabinoids** at 651K¹, although temperature dependence and specific mechanism not yet determined

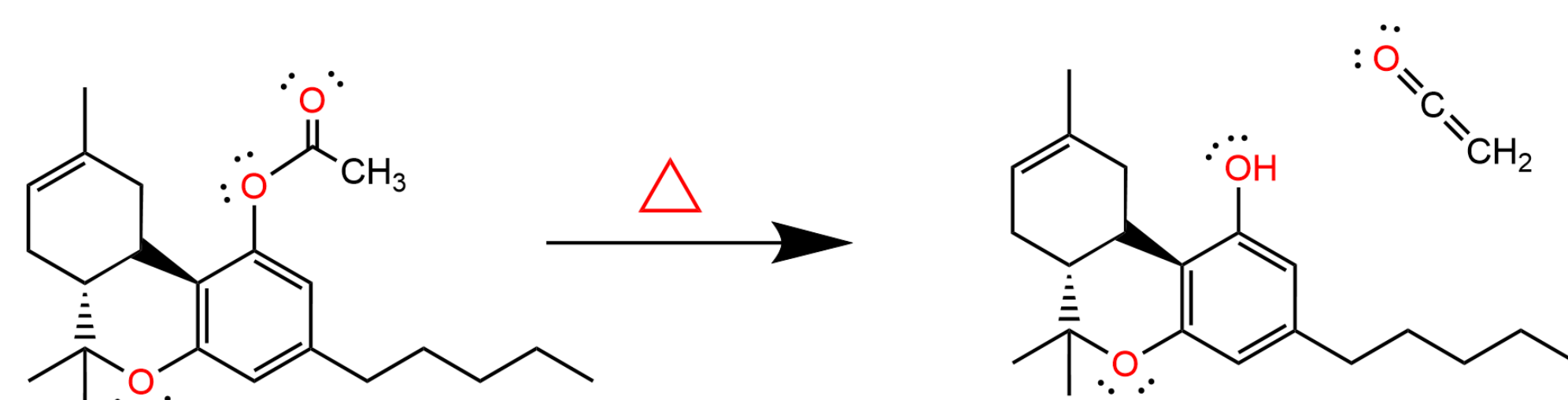


Figure 2. Heat catalyzed elimination of ketene from delta-8 tetrahydrocannabinol acetate.

- Study in 2020 by Wu and O'Shea found a related mechanism for the elimination of **ketene** in phenyl acetate and vitamin E which proceeded **through a 4 membered ring concerted pathway**²

Methodology & Computational Details

Reaction Mechanism

- Determine the lowest energy transition state and reaction pathway for the elimination of **ketene** from **CBNo** and **delta-8 THCo**
- Transition state search to find saddle point from optimized product structure, confirmed by presence of imaginary vibrational frequency

Temperature Dependence

- Determine the temperature dependence of **ketene** formation in **delta-8 THCo** and **CBNo** with special emphasis on comparing rates of manufacturer recommended temperatures and those found in the by Munger et al.
- Temperatures range tested from 298 K to 5000 K

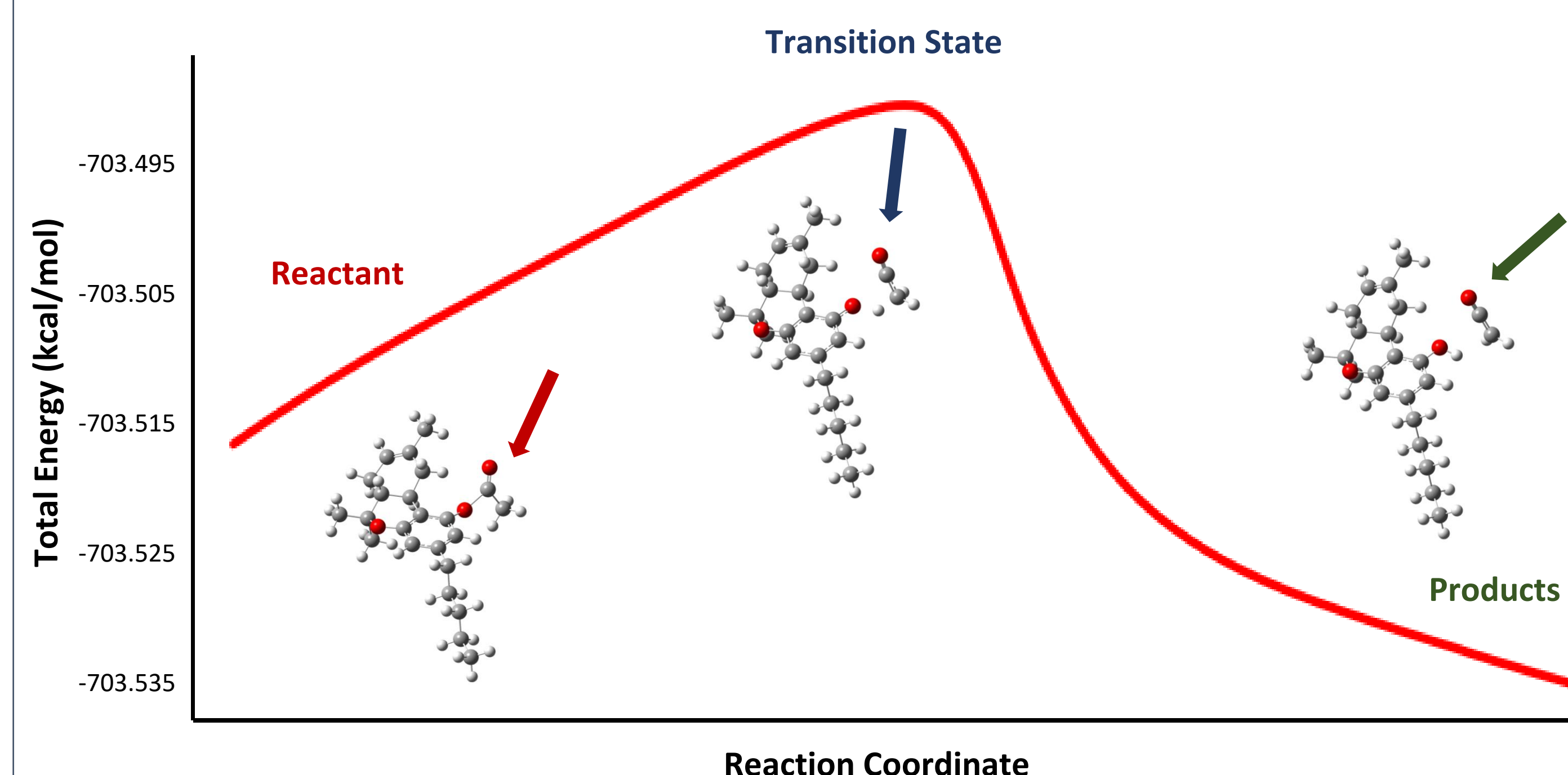
Gas Phase vs Liquid Phase

- Determine the impact of liquid vs gaseous environment on reaction rate

Computational Details

- Gas systems will utilize density functional theory with M062X and B3LYP functionals, all DFT functionals will utilize a 6311-G basis set with with (d) polarization function and one set of diffuse s and p function on heavy atoms. Systems utilize XQC SCF algorithm with ultrafine integration grid
- Liquid systems utilize explicit solvent modeling with M062X for reactant and UFF for solvent molecules. Basis set, polarization function, and diffuse functions are the same as gas

Reaction Mechanism



Thermodynamics

- We observed that this reaction is **endergonic** under standard conditions and thus does not favor the formation of **ketene**

Kinetics

- We observed the elimination of **ketene** from **delta-8 tetrahydrocannabinol acetate** to not proceed through a synchronous four membered transition ring, instead we observed a **concerted asynchronous pathway**
- The reaction involves decrease of electron density between carbon and oxygen, shortly **followed** by an asynchronous proton transfer
- The pathway observed was **different** than the related eliminations of **ketene** from vitamin E and phenyl acetate observed by Wu and O'Shea

Temperature Dependence

Activation Energy (Gas Phase)

- We observed a significant decrease in activation energy associated with increased temperature for all functionals tested

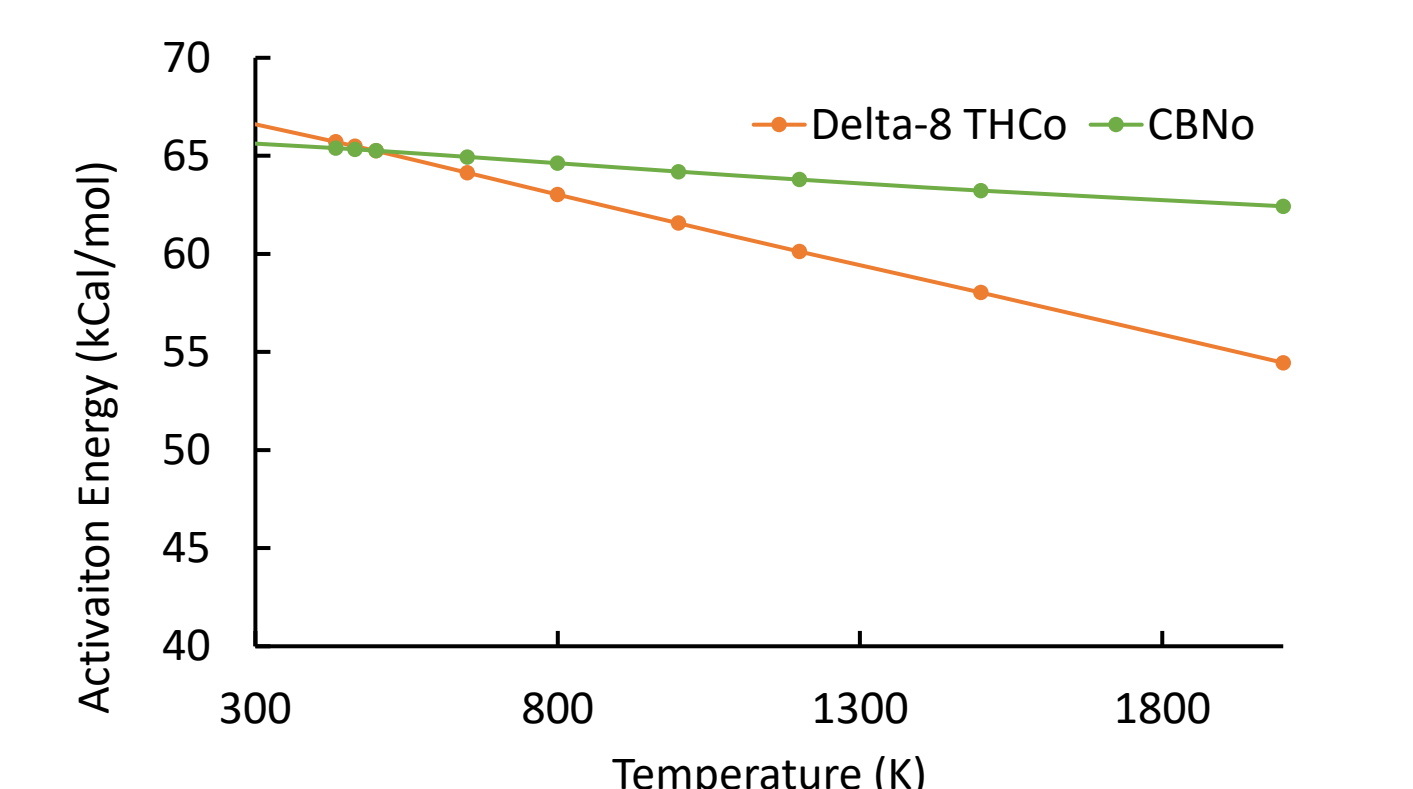
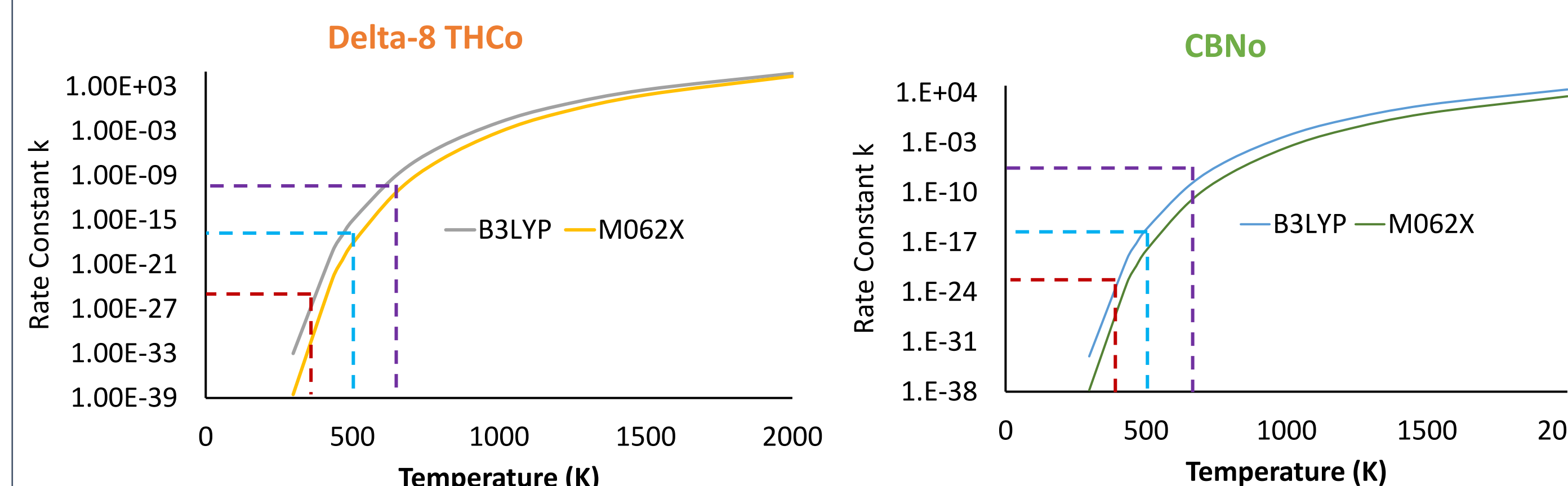


Figure 3. Activation energy of transition state from reactant with B3LYP functional over various temperatures.

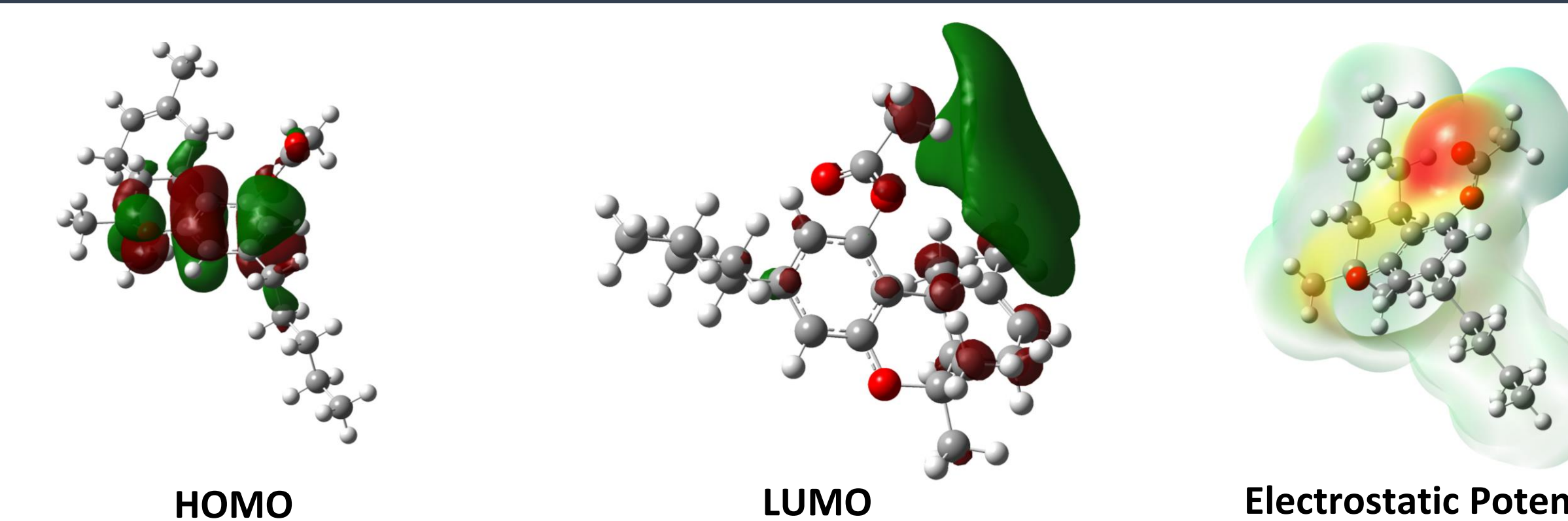
Rate Constant (Gas Phase)

- We observed temperature dependence for the rate constant for both **cannabinoids**. The **rate** of elimination of **ketene** is directly proportional to the **rate constant**.



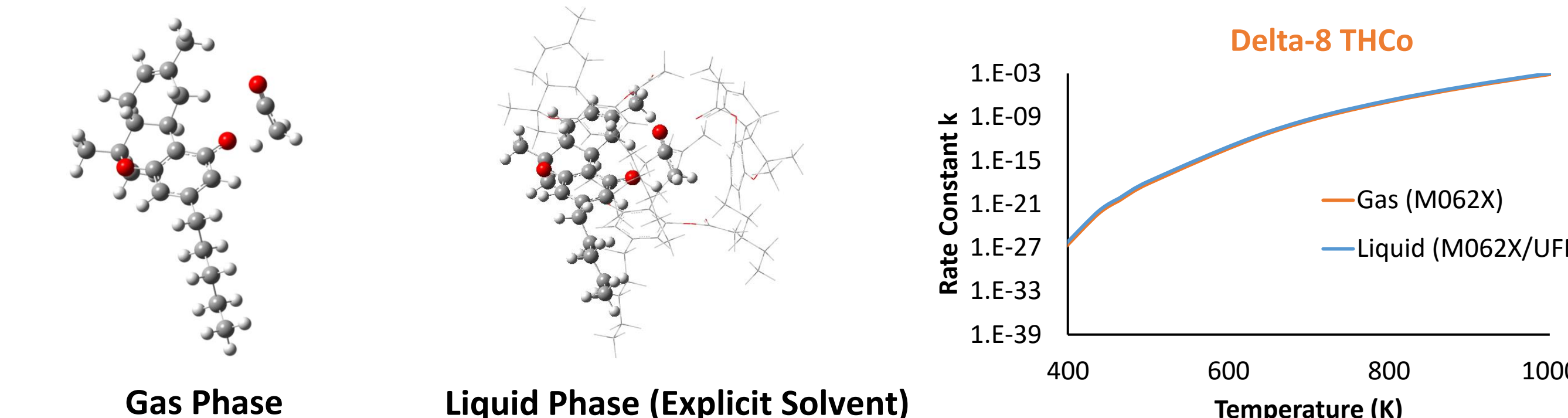
- Ketene** forms $\sim 10^{10}$ - 10^{12} **faster** at a given concentration of cannabinoid between a "low temperature" (**433 K**)⁴ and temperature tested by Munger et al. (**651 K**)¹
- Ketene** forms $\sim 10^6$ - 10^7 **faster** at a given concentration of cannabinoid between a "very high temperature vaporizer" (**500K**)⁴ and the temperature tested by Munger et al.

MO, ESP, Gas vs Liquid



Gas vs Liquid | Rate Constant

- We observed a slight increase in **rate constant** for **delta-8 THCo** (and associated reaction rate) for this transition simulated in a **liquid phase** compared to a **gas phase**.



Conclusions

Reaction Mechanism

- The data obtained suggest that the reaction is reactant (**acetylated cannabinoid**) favored
- The data additionally suggest the reaction proceeds through an asynchronous concerted mechanism

Temperature dependence

- Ketene** formation rate appears to increase dramatically for both **delta-8 THCo** and **CBNo** with temperature, a difference of $\sim 10^{10}$ between a recommended low temperature and the temperature tested by Munger et al.

Phase dependence

- We observed a slight increase in reaction rate for **delta-8 THCo** in the explicit liquid phase simulation compared to the gas phase simulation.
- Due to the high temperatures required to undergo the formation of **ketene** (high activation energy), it is likely the gas phase transition is predominant

Future Directions

- We would like to test more specific temperatures that are commonly found in commercial vaporizer products
- We would like to determine the impact of using different relevant functionals (MP2, double hybrid onium, ect...). MP2 is almost converged and looks promising!
- We would also like to study this reaction with other acetylated cannabinoids (HHCo, HHCpo, CBD-(OAc)₂)

DISCLAIMER: This research should not be used to determine the safety of inhaling acetylated cannabinoids, it is a simulated model which is subject to error. We do not condone or encourage the of vaping or use of any substance.

Acknowledgements:

Thank you to Dr. Shubin Liu and the University of North Carolina at Chapel Hill for your help in making this project possible, also thank you to the team behind Gaussian 16⁵

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