Computational Investigations of Intermolecular Diels-Alder Reactions of α-amido acrylate dienophiles
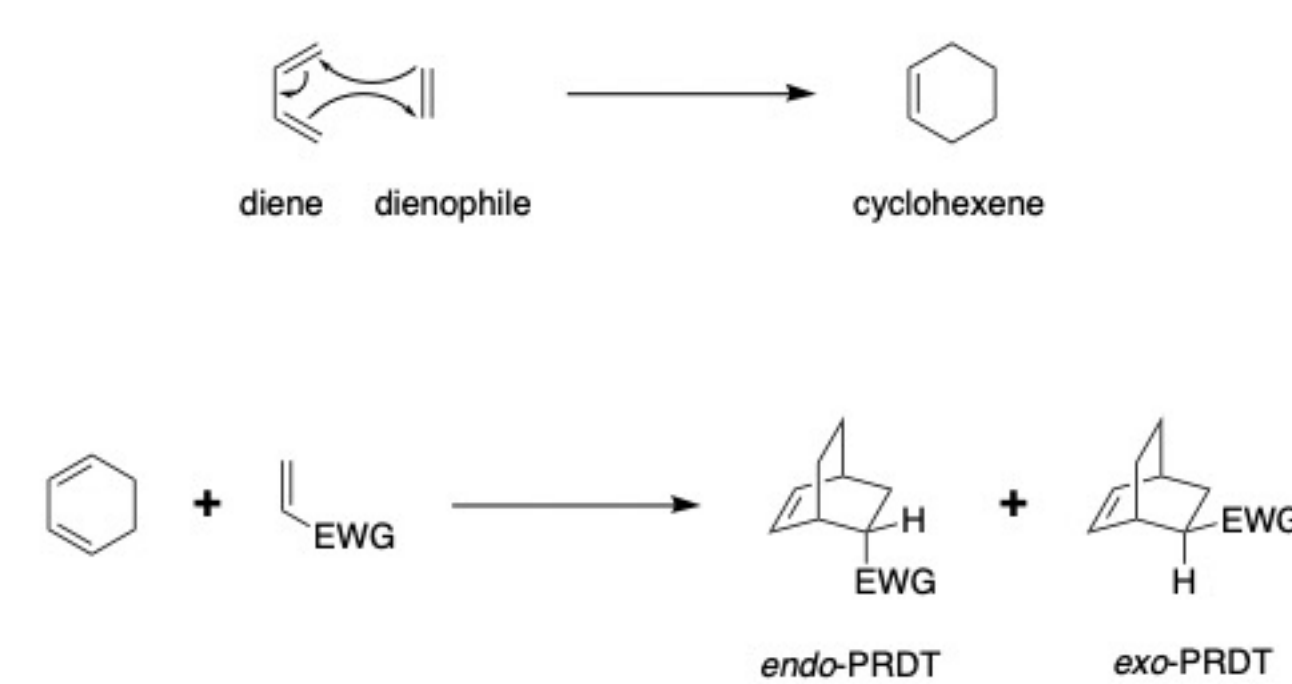
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## Intermolecular Diels-Alder Reactions Review

The Diels–Alder reaction has been a practical tool in the field of synthetic organic chemistry since its discovery in the 1950's. During the reaction, a diene and dienophile come together to form a substituted six membered ring. It is a pericyclic reaction, specifically a [4+2] cycloaddition. Due to its prevalent use in synthesizing a wide variety of products, achieving a better understanding of a product's preferred stereochemistry is a worthwhile endeavor.

O. Diels, K. Alder, *Justus Liebigs Ann. Chem.* 1928, 460, 98– 122

Klein, D. R. *Organic Chemistry*; John Wiley & Sons, 2017.

Endo vs. Exo Formation Preference Conditions
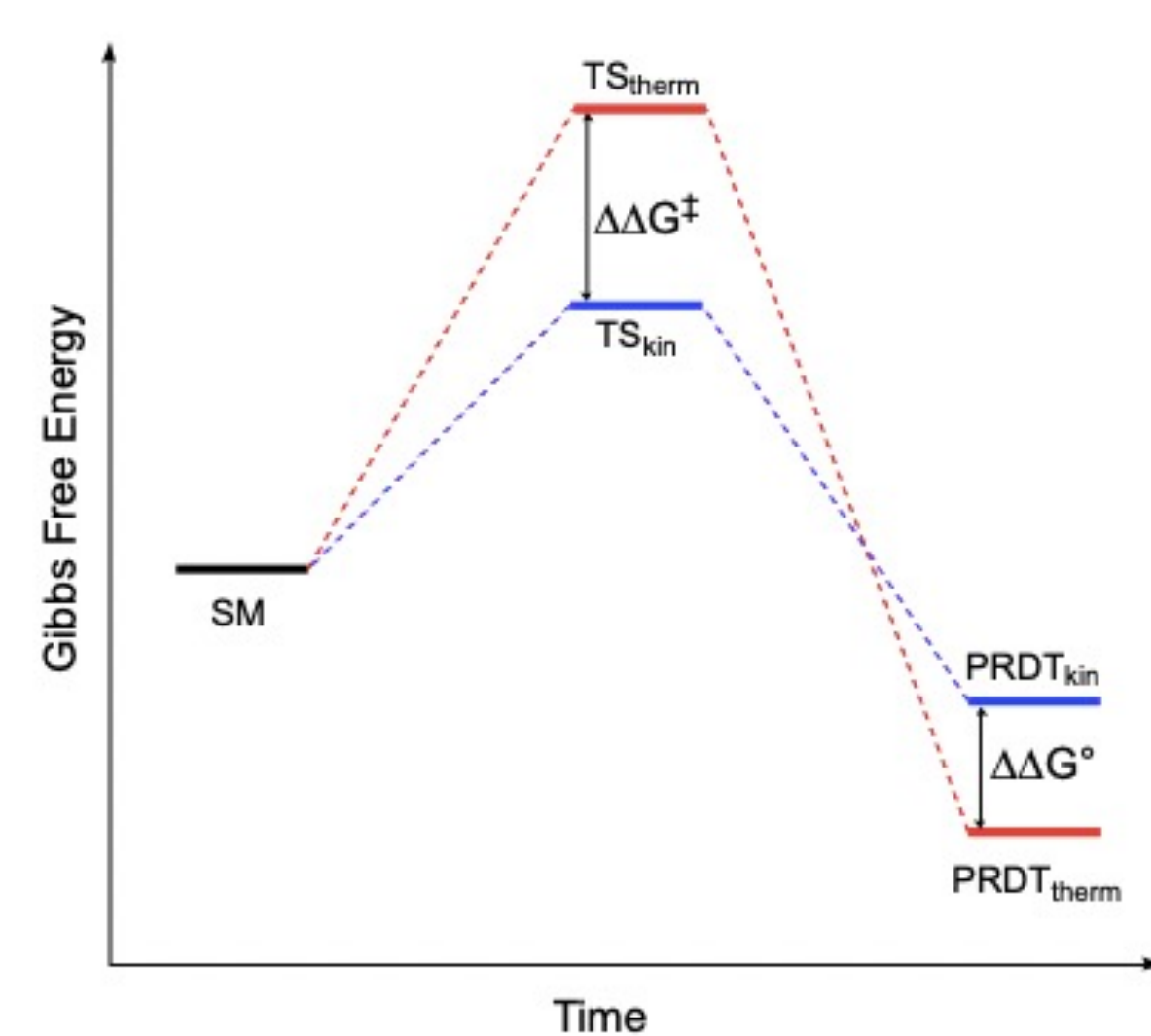
In most scenarios, the endo product is favored over the exo. This is due to the tendency of the endo product's transition state to have a lower free energy than that of the exo product. However, if the conditions of the reaction are altered such as upon the addition of heat, the exo product can be isolated at a higher ratio than in previous conditions. This is due to the exo product being more thermodynamically stable than the endo product. Running computational calculations enables determination of the preferred product of specific reactions.

Klein, D. R. *Organic Chemistry*; John Wiley & Sons, 2017.

Building off Spivey's Research

Synthetic Diels–Alder reactions were run in the lab by Spivey *et al.* where α-Amido acrylates were reacted with N-Cbz-1,2-dihydropyridine and cyclopentadiene. The products of these reactions were examined to decipher which elements dictate their endo/exo selectivity. When running the reactions with cyclopentadiene, the endo products dominated. In order to increase the exo product yield, multiple Lewis acids were added to the reactions. In an effort to expand the synthetic scope of an underdeveloped class of dienophiles, analyze endo/exo selectivity, and increase reaction predictability computational research was conducted. The cyclizations displayed to the left represent the reactions investigated. The setting for the density functional calculations were chosen based off prior research.

Abas, Hossay, Christopher S. Frampton, and Alan C. Spivey. 2016. "Diels–Alder Reactions of α-Amido Acrylates with N-Cbz-1,2-Dihydropyridine and Cyclopentadiene." *The Journal of Organic Chemistry* 81 (20): 9947-56. https://doi.org/10.1016/j.ejpb.2015.06.007.

Sizemore, N.; Heil. E. *Journal of the Pennsylvania Academy of Science* 2019, 93, 118–131.

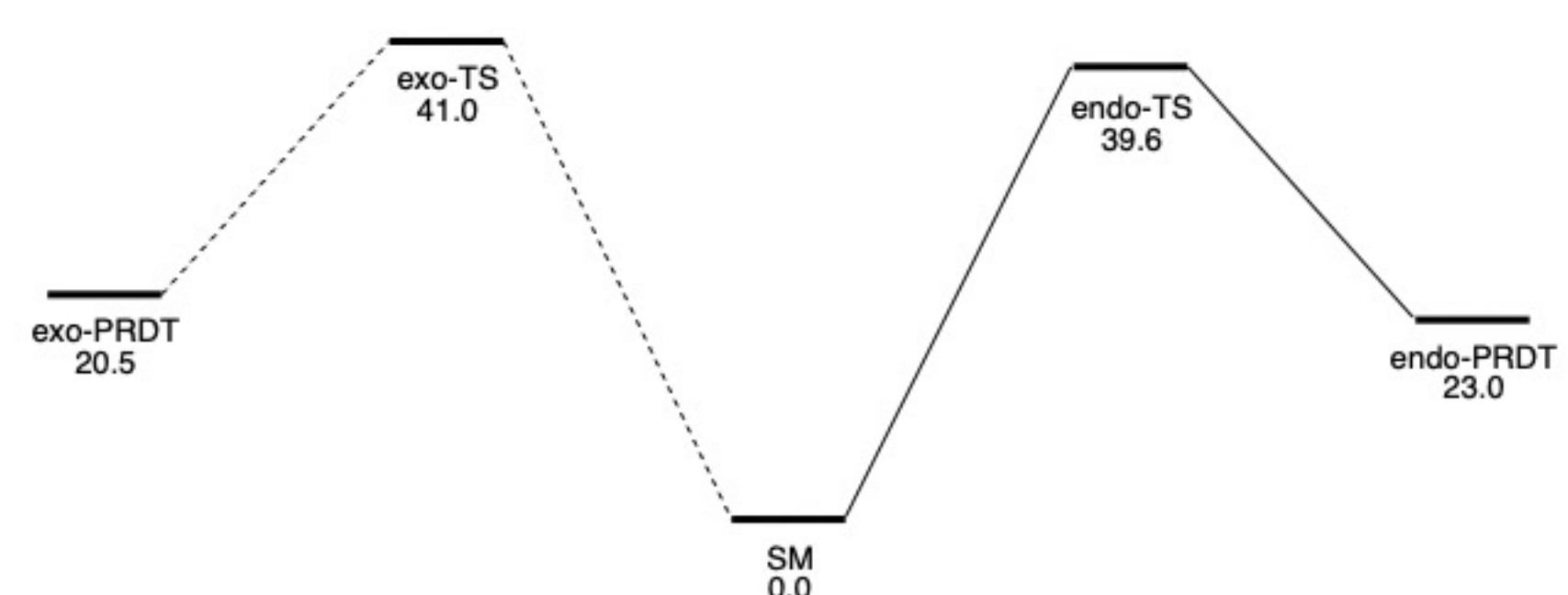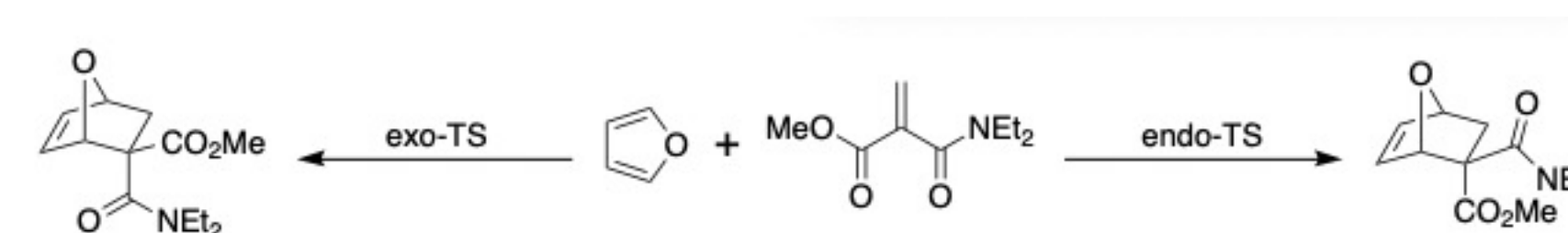## Computational Calculation Road Map

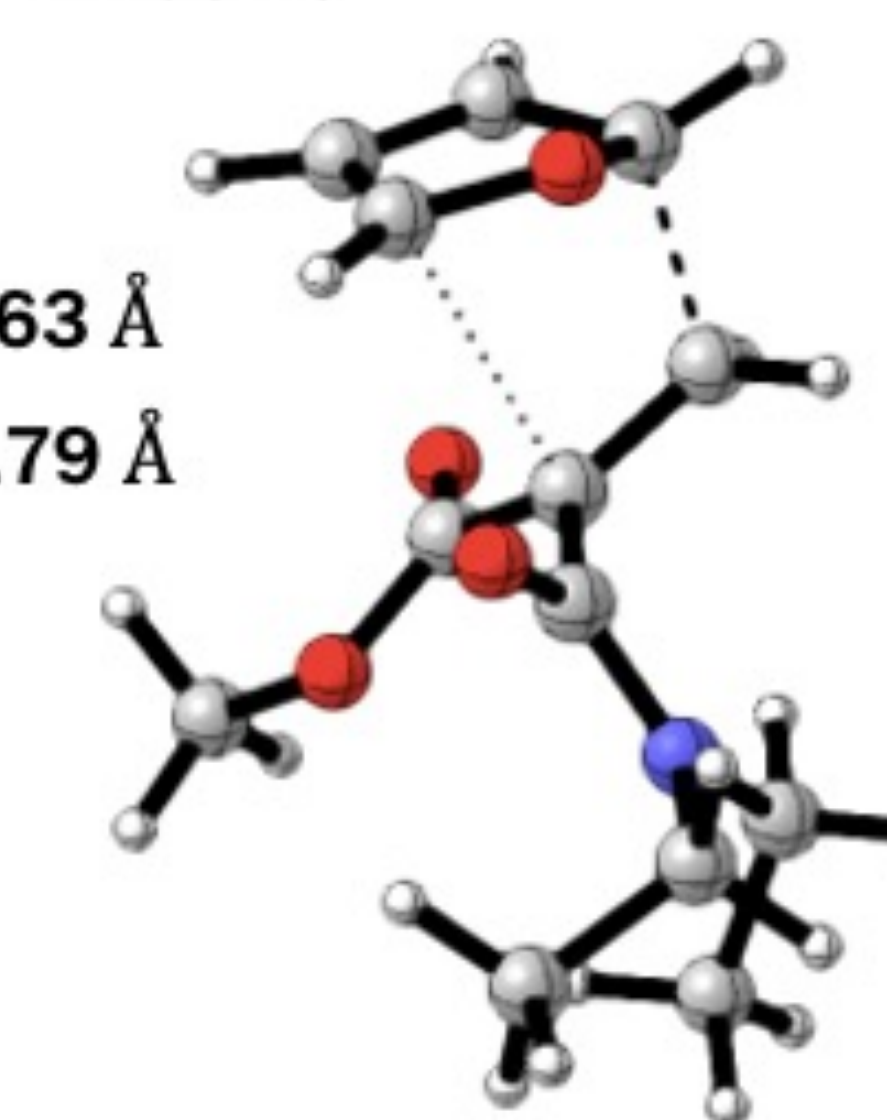### Spartan

Gaussian

Cyclization of Dienophile 6A with Furan

Free energy diagram constructed from calculations run in Gaussian16 using B3LYP, 6-31+G(d). All values are given in kcal/mol.
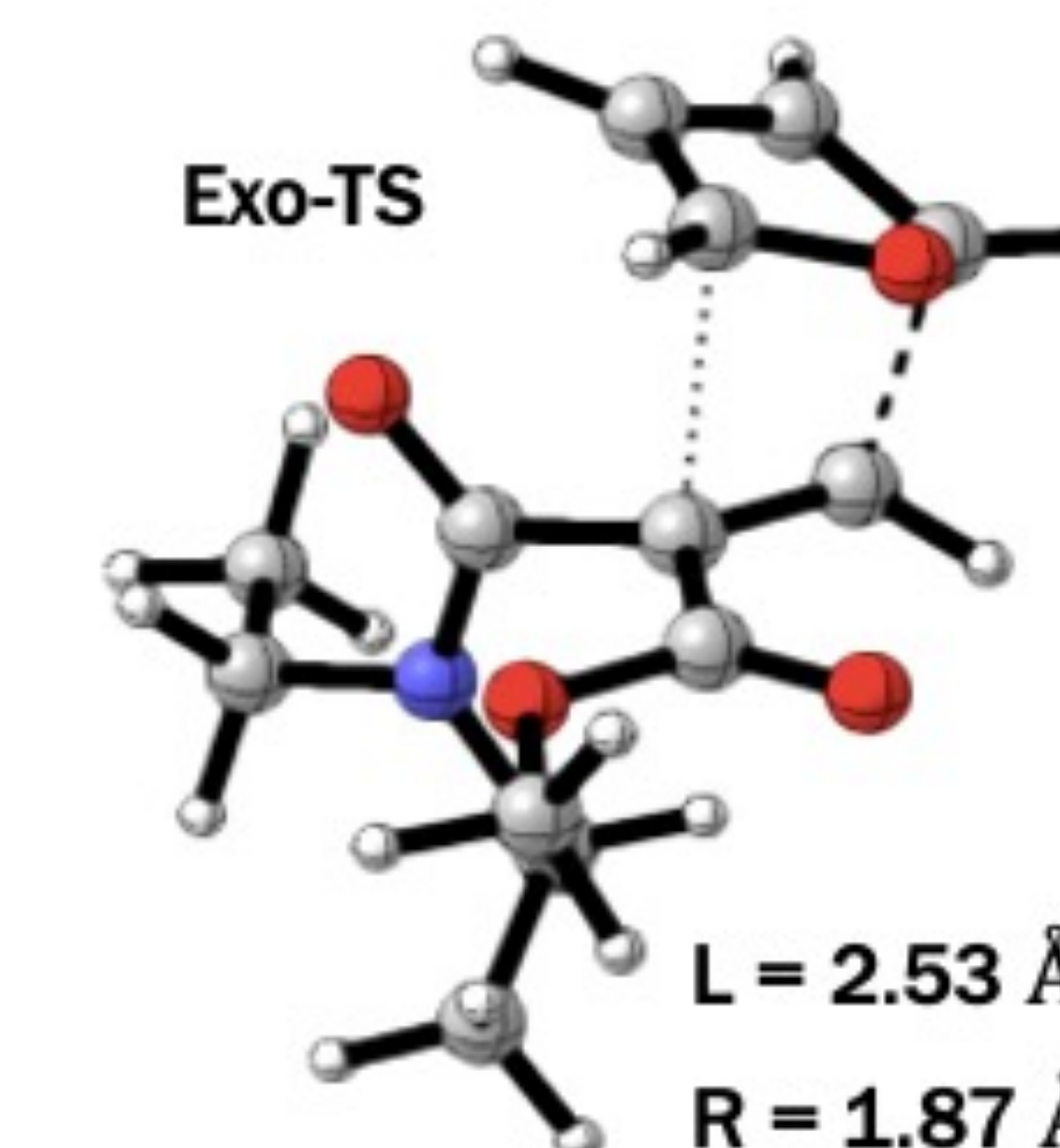

Transition state conformations for endo and exo conformations of dienophile 6A. New C–C bond formations are depicted with dotted lines.

Data for ongoing calculations

Dienophile	Transtition State Free Energy		Product Free Energy	
	Endo	Exo	Endo	Exo
(structure)	40.04	40.77	21.69	20.47
(structure)	39.68	39.77	23.83	21.89

Raw data from the successive cyclizations are shown above, the last poses for each cyclization are currently being run through Gausian16. Differences in energy are given in kcal/mol.

Preliminary Conclusions and Future Work

Based off currently available data, endo product formation is favored for each cyclization while the exo product has a lower free energy. Both characteristics support traditional hypotheses about endo/exo product formation under kinetic and thermodynamic control. Once all files are run through Gaussian16, IRC calculations will be run on the lowest energy poses to ensure validation. In addition, an identical set of calculations will be run on another cyclization featuring dienophile 6A and a siloxy diene in order to compare energy values between use of the siloxy diene versus the furan.