



A Computational Investigation of Energetics in Diels-Alder Reactions Using Vinyl Sulfone Derivatives

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Introduction

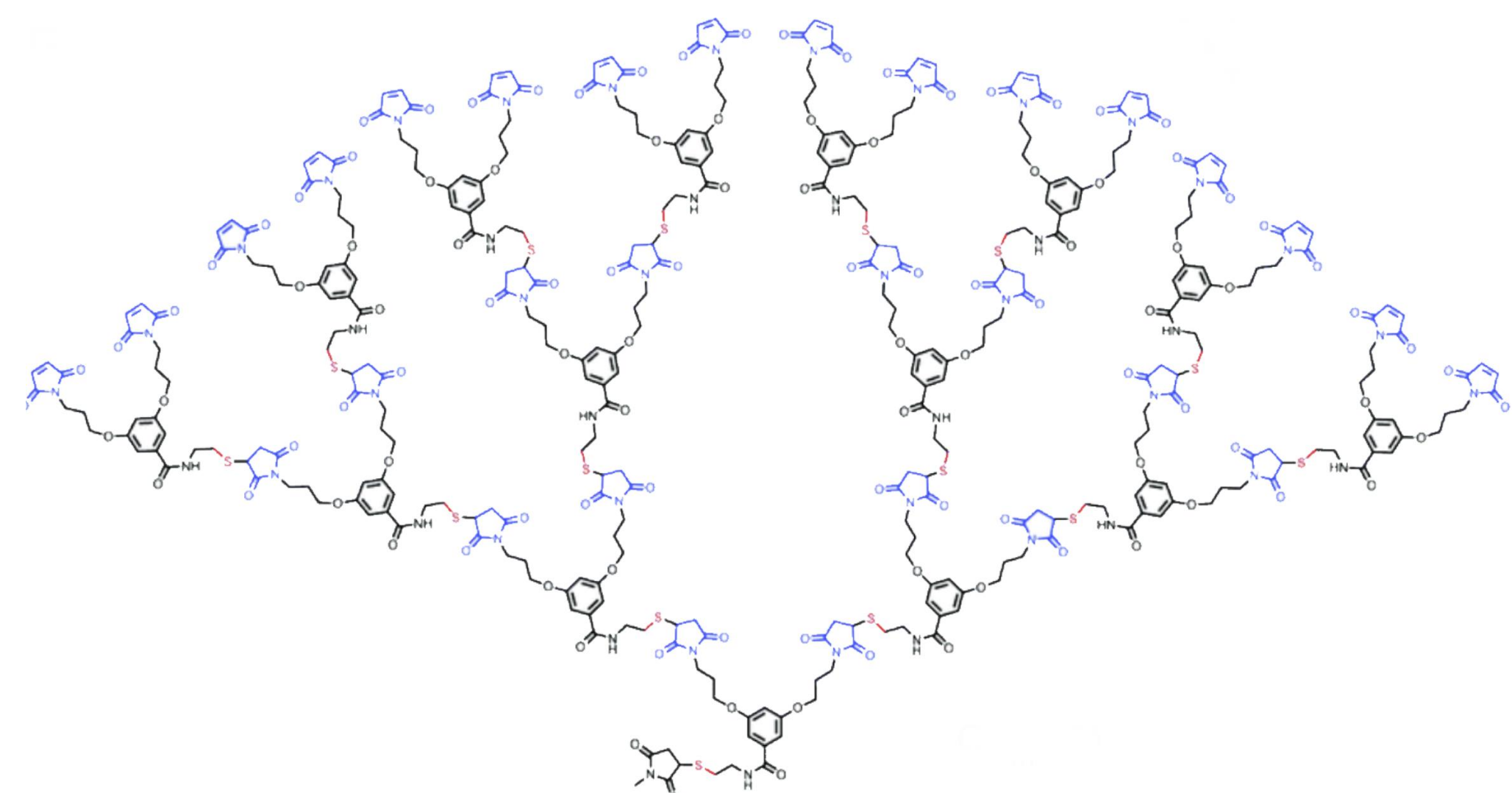


Figure 1: Dendrimers synthesized using furan-maleimide derivatives³

- ❖ Dendrimers: highly branched macromolecules used in drug delivery, tissue engineering and the design of specialty polymers.
- ❖ Traditionally synthesized using acid/base chemistry
- ❖ Recently, Diels-Alder synthesis methods have been investigated due to their multiple advantages
- ❖ Some Diels-Alder reactions are a type of dynamic covalent chemistry, meaning they undergo thermodynamically reversible covalent bond formation; this allows for protecting groups to be added and removed without the creation of byproducts using heat
- ❖ Furan boils at 30 degrees Celsius, allowing it to be removed easily

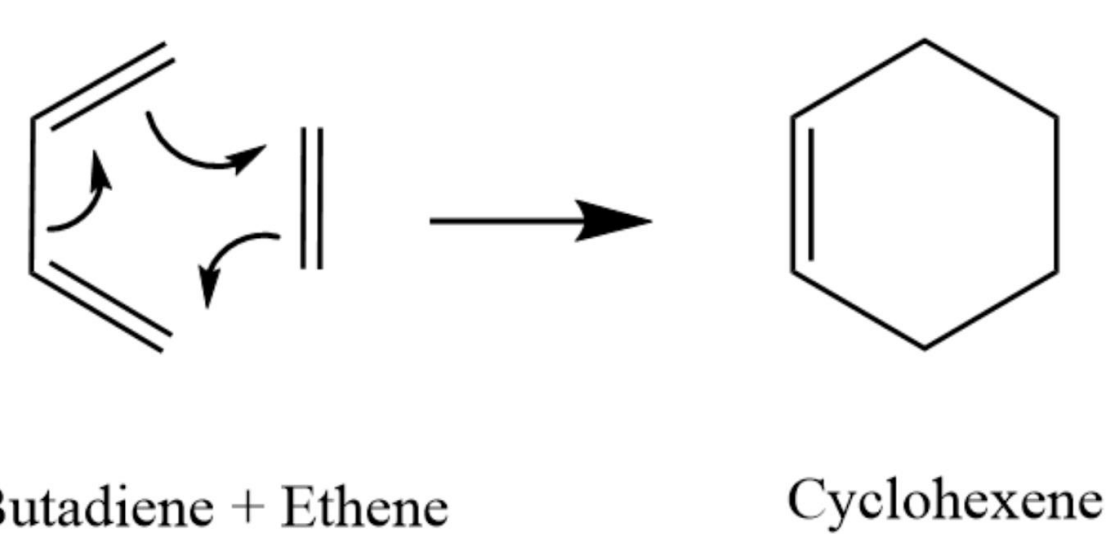


Figure 2: General Diels-Alder reaction between butadiene and ethene

- ❖ Dendrimer formation from Furan-maleimide derivatives studied by Stephen Frayne, PhD³
- ❖ Led to insoluble dendrimers- insolubility limits dendrimer growth and practical applications
- ❖ Dendrimers also had chiral centers

Motivations and Methods

- ❖ Investigation of methyl vinyl sulfone derivatives, a possible alternative to furan-maleimide proven to create dendrimers that are more soluble and do not have chiral centers (which limits the number of possible products)²
- ❖ Studied four different dienes in a reaction with vinyl sulfone dienophile: furan, dimethyl fulvene, thiophene and cyclopentadiene
- ❖ Calculated ΔH° and ΔG° for overall reaction and transition states in gas phase, chloroform (CHCl_3) and DMSO ($\text{C}_2\text{H}_6\text{OS}$)
- ❖ Computations performed at the B3LYP/6-31G(d), M062x/6-311G(2d,p), wB97xd/6-311G(2d,p) and CBS-QB3 levels of theory using the program Gaussian16

Energetics of Vinyl Sulfone Diels-Alder Reactions

1. Reaction Scheme Overview

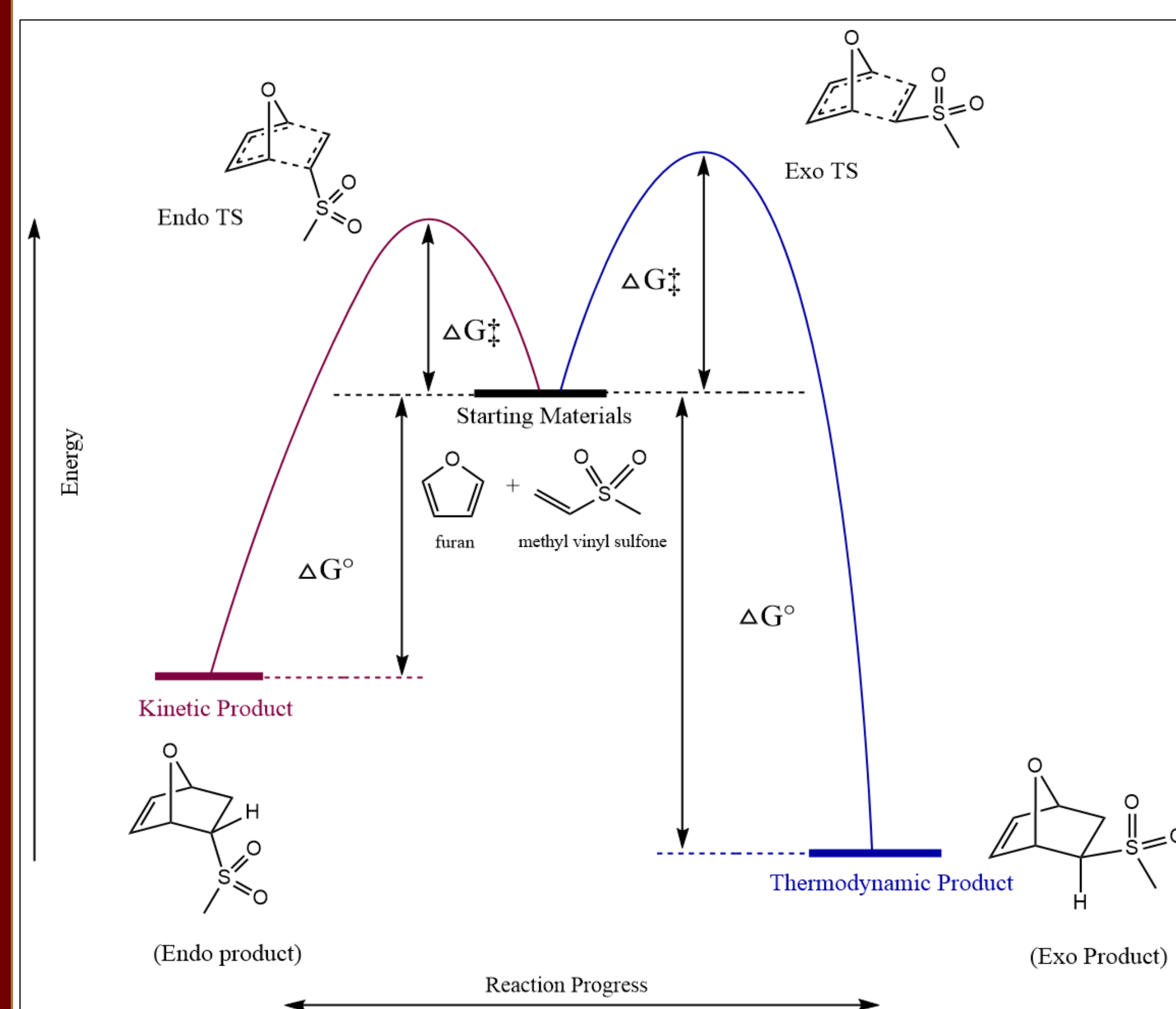


Figure 3: Reaction scheme for Diels-Alder reaction between furan (diene) and methyl vinyl sulfone (dienophile)

Diene	Endo Product	Exo Product
Furan	Gas Phase	Thermodynamic + Kinetic
	Chloroform	Kinetic
	DMSO	Kinetic
Cyclopentadiene	Gas Phase	N/A
	Chloroform	Kinetic
	DMSO	Kinetic
Thiophene	Gas Phase	Thermodynamic + Kinetic
	Chloroform	Thermodynamic + Kinetic
	DMSO	Thermodynamic + Kinetic
Dimethylfulvene	Gas Phase	
	Chloroform	N/A
	DMSO	Kinetic

Figure 4: Diene structures and table displaying the corresponding thermodynamic and kinetic products for each reaction

2. Transition State and Reaction Free Energy

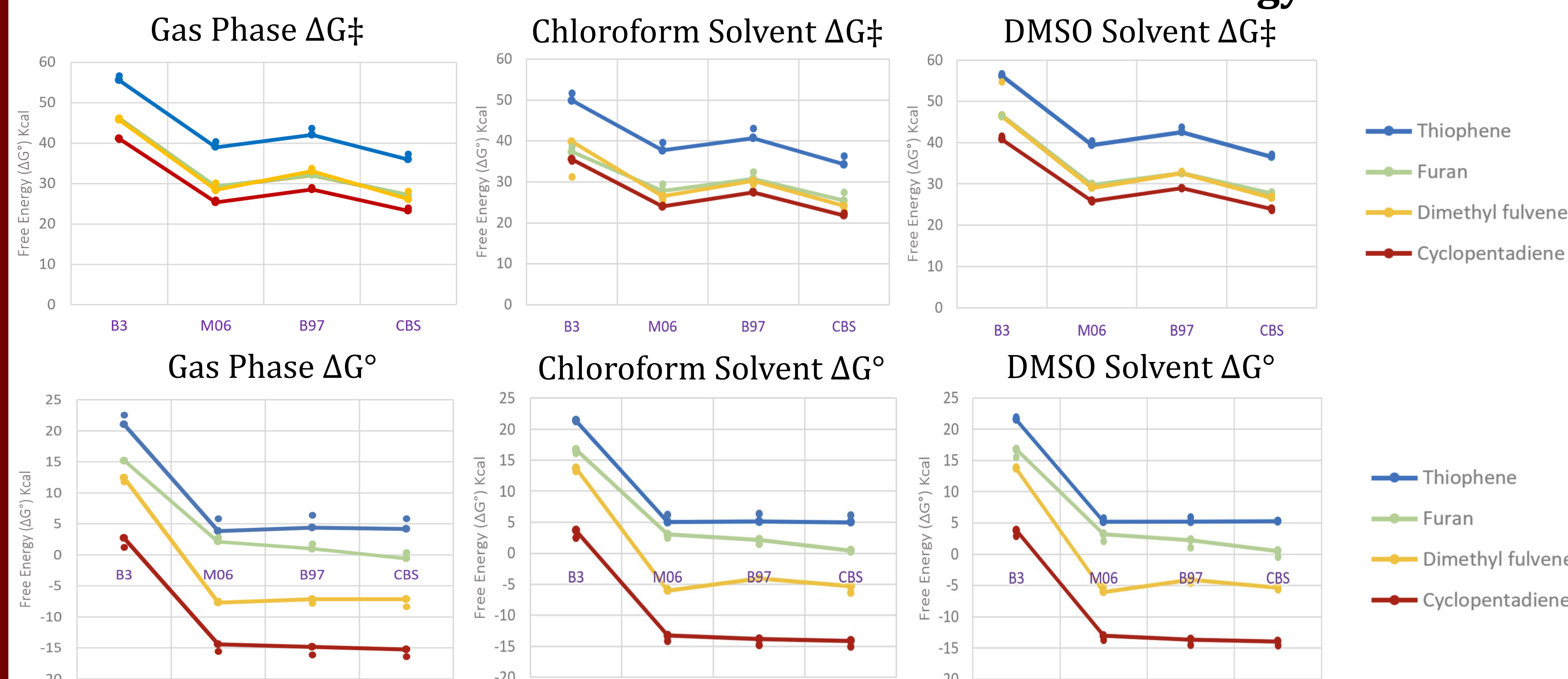


Figure 5: Graphs of both endo and exo product overall reaction and transition state free energies at the B3LYP/6-31G(d), M062x/6-311G(2d,p), wB97xd/6-311G(2d,p) and CBS-QB3 levels of theory

- ❖ B3LYP level of theory produces outlier values
- ❖ CBS expected to be closest to experimentally derived values

- ❖ Furan and dimethyl fulvene have ΔG values closest to 0 \rightarrow most likely to be reversible reactions

Comparison of Maleimide and Vinyl Sulfone ΔG°

Furan-Maleimide	ΔG°	ΔG^\ddagger
Endo	-1.5	22.5
Exo	-4.5	22.7

Furan-Methyl Vinyl Sulfone	ΔG°	ΔG^\ddagger
Endo	0.42	27.1
Exo	0.24	28.0

Figure 6: ΔG° values for furan-maleimide reaction MP2/6-311+G(d,p) level of theory in CH_3N solvent and furan-methyl vinyl sulfone reaction at CBS-QB3 level of theory in chloroform (CHCl_3) solvent¹

- ❖ ΔG° of furan-methyl vinyl sulfone reaction is less favorable than furan-maleimide \rightarrow there will most likely be less Diels-Alder product at equilibrium
- Adding excess furan would drive reaction towards product formation
- ❖ Vinyl sulfone reaction has a higher ΔG^\ddagger , meaning the reversibility of the reaction will most likely be slower

3. Molecular Orbital Analysis

Magnitude of HOMO/LUMO Gap

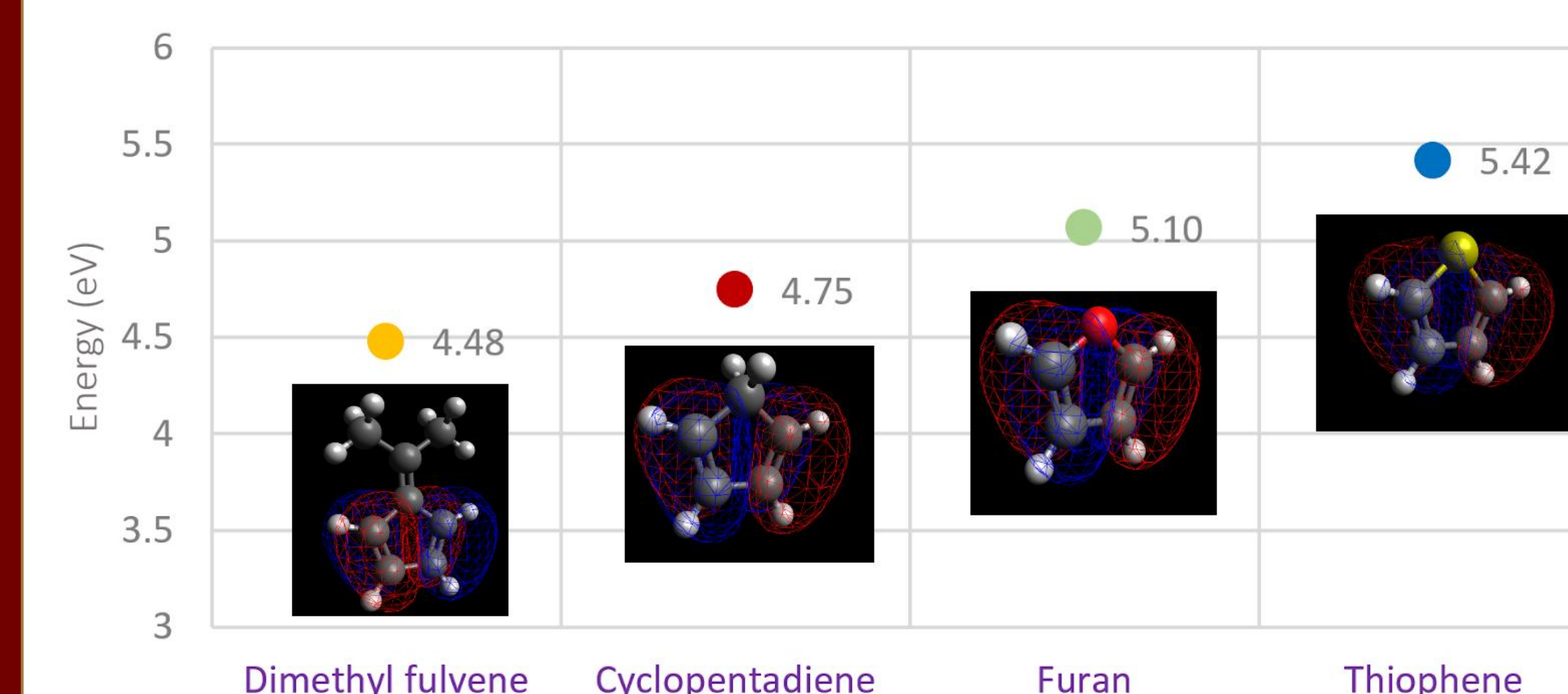


Figure 7: Visualization of HOMO orbitals of cyclic dienes and the magnitude of the HOMO/LUMO gap between each cyclic diene and the methyl vinyl sulfone dienophile.

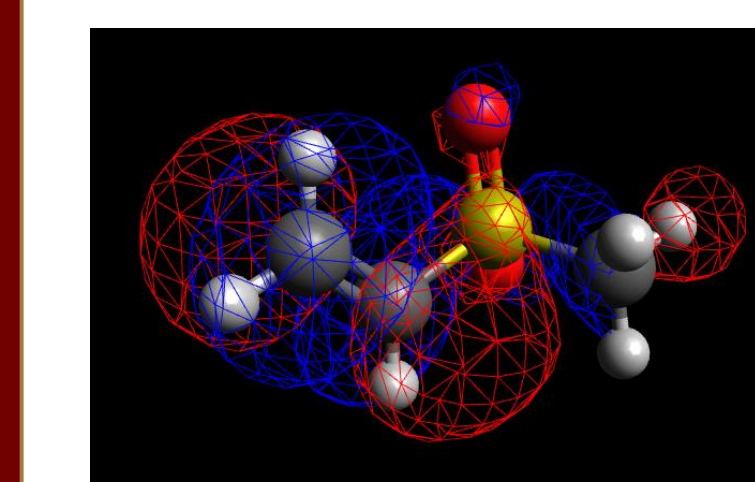
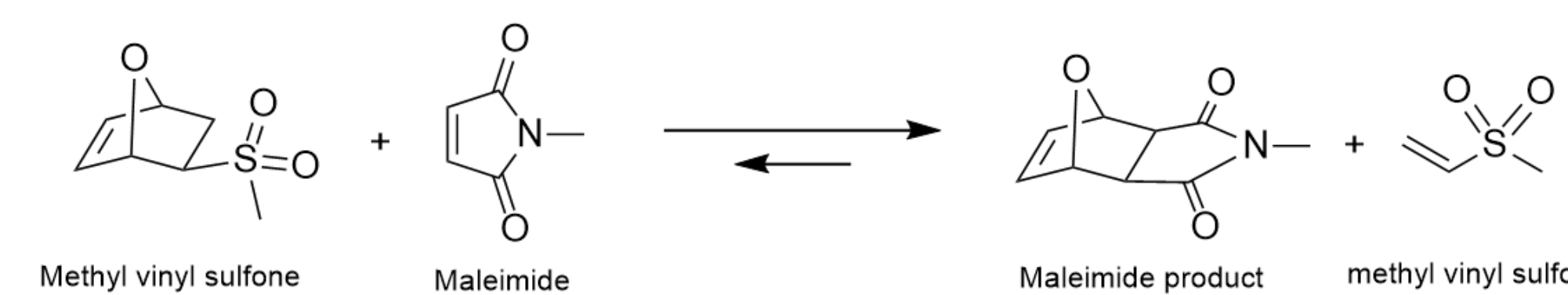


Figure 8: LUMO visualization of methyl vinyl sulfone dienophile

- ❖ In Diels Alder reactions, LUMO of electrophilic dienophile typically reacts with HOMO of electron-rich diene
- ❖ Closer HOMO/LUMO orbitals often make a reaction more favorable
- ❖ Dimethyl fulvene and cyclopentadiene are more favorable (from ΔG values), also have smallest HOMO/LUMO gap

Future Directions

- ❖ Performing reactions and calculating experimental free energy and enthalpy values for furan and dimethyl fulvene reactions
- ❖ Investigating which level of theory most accurately predicts free energy and enthalpy values
- ❖ Experiments to confirm favorability of furan maleimide over furan vinyl sulfone reaction



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References

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