The Determinants of *Endo* and *Exo* Selectivity in Diels-Alder Reactions of Maleic Anhydride: A Theoretical Study
The Determinants of *Endo* and *Exo* Selectivity in Diels-Alder Reactions of Maleic Anhydride: A Theoretical Study

Disclosed close to a century ago, the Diels-Alder reaction remains one of the most important reactions in synthetic organic chemistry. Despite its age and usefulness, a clear picture of driving forces behind the reaction’s endo or exo selectivity remains to be found. DFT-B3LYP/6-31G computations on the maleic anhydride-furan reaction (reaction 1) and the maleic anhydride-1,3-cyclohexadiene reaction (reaction 2) confirmed the *endo* product is favored in the short-run. Long-run analysis showed the possible accumulation of *exo* product in reaction 2. Experimental tests verified these assumptions. Here, we describe a complete thermodynamic and kinetic picture of these two reactions. These insights provide a richer understanding of the factors behind endo and exo preference and will enable the application of structural computational methods to help synthetic chemists better control selectivity.

The Diels-Alder reaction is a [4+2] pericyclic reaction involving a diene and a dienophile\(^1\). Originally discovered by Otto Paul Hermann Diels and Kurt Alder in 1928, it immediately became one of the most useful reactions in organic chemistry because of the stereospecific ring forming mechanism\(^2\)–\(^5\) (Figure 1). As a result of this mechanism, it is possible to form two different products with the same reactants in more complex variants of the Diels-Alder reaction\(^6\). These two products are called the *exo* and *endo* product. The *exo* product is generally thermodynamically favored because of fewer steric clashes in the product\(^7\) while the *endo* is the kinetically favored. Alder and Stein first suggested the *endo* preference was due to the maximum accumulation of double bonds, implying the existence of attractive forces\(^8\)–\(^11\). The Alder-Stein rule holds that the *endo* product should be the only observed product\(^12\). Woodward and Hoffmann instead proposed the idea of secondary orbital interaction, which is now the accepted theory\(^13\),\(^14\),\(^15\). Recently, this idea has come under scrutiny with dispersion and steric forces proposed to be involved\(^16\),\(^17\). Today, the determinants of *endo* and *exo* selectivity still remain controversial\(^17\)–\(^21\). Yet these determinants are one of the most important components of the Diels-Alder reaction\(^22\),\(^23\). Further clarifying research on this topic may have enormous consequences for synthetic organic chemistry and, thus, drug discovery\(^24\),\(^25\).

In order to investigate the thermodynamic, kinetic, and molecular driving forces of this phenomenon, computational chemistry techniques were performed on the reaction of furan (1) and maleic anhydride (2), and the reaction of 1,3-cyclohexadiene (4) and maleic anhydride (2) (Figure 2). Experimental work served as a control.

The cycloaddition of maleic anhydride and furan remains a model reaction for *endo* and *exo* selectivity. Previous studies have focused on its stereochemistry and orbital...

*Keywords:* Diels-Alder reaction, density functional theory, thermodynamics, kinetics

*Correspondence to:*
interactions\textsuperscript{6,16,18,26}. There is, however, little in the way of a comprehensive thermodynamic and kinetic study of the reaction. The reaction of 1,3-cyclohexadiene with maleic anhydride is even less well studied even though it is quintessential reaction in organic chemistry. There remain no studies that deal with its thermodynamic and kinetic properties. Both reactions have normal electron demand, in which an electron-poor dienophile’s lowest unoccupied molecular orbital (LUMO) reacts with an electron-rich diene’s highest occupied molecular orbital (HOMO)\textsuperscript{17}. It is important to note that furan is more electron rich that 1,3-cyclohexadiene.

Experimental procedure followed the literature\textsuperscript{12}. Computational work used molecular geometry optimizations with analytical frequency calculations performed at the DFT-B3LYP/6-31G level of theory using Gaussian09 and GaussView 5. The QST3 method was employed at the same level of theory for the transition state search.

While the Diels-Alder reaction is seen as a relatively simple and elegant reaction, the simple part of this description is often not accurate. This report elucidates some of the controls behind endo and exo selectivity by presenting a comprehensive thermodynamic and kinetic picture of these two model reactions in addition to a molecular description of the reaction.

**Thermodynamics and Kinetics of the Products**

An exploration of the thermodynamics and kinetics of the two reactions must start with a comparison of the driving forces for each reaction. These characteristics will better explain the different endo-exo selectivities of the two reactions.

There are three key factors that need to be considered: enthalpy (H), entropy (S), and Gibbs free energy (G). The free energy component is also perhaps the most important term as it determines whether a reaction will actually happen ($\Delta_r G < 0$), simplifying the analysis into what is affecting $\Delta_r G^\circ$. This term can be thought of as the combination of the enthalpy and the entropy with a temperature dependent term.

$$\Delta_r G^\circ = \Delta_r H^\circ - T\Delta_r S^\circ$$  \hspace{1cm} (1)

**Entropy**

Looking at the entropy data, it appears that the entropies of the curves are largely the same (Figure 3A). Quantitatively, the entropy of activation and the entropy of reaction for all the reactions lie within 0.001 kcal/(mol*K) of each other (Table 1). Compared to the differences in

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**Figure 2: The reactions under study.** Reaction 1 is the formation of endo-3 or exo-3 from furan (1) and maleic anhydride (2). Reaction 2 is the formation of endo-5 or exo-5 from 1,3-cyclohexadiene (4) and maleic anhydride (2)
**Figure 3:** Reaction curves for the endo and exo pathway of reaction 1 and reaction 2: A) the change in entropy, B) the change in enthalpy, C) the change in free energy.

**Table 1:** A comprehensive table of thermodynamic and kinetic parameters for the endo and exo pathways of reaction 1 and 2 at STP.

<table>
<thead>
<tr>
<th></th>
<th>$\Delta^{\ddagger}S$</th>
<th>$\Delta S^\circ$</th>
<th>$\Delta^{\ddagger}H$</th>
<th>$\Delta H^\circ$</th>
<th>$\Delta^{\ddagger}G$</th>
<th>$\Delta G^\circ$</th>
<th>$E_a^\ddagger$</th>
<th>$E_a^\circ$</th>
<th>$k_f$</th>
<th>$k_r$</th>
<th>$K_{eq}$</th>
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<tbody>
<tr>
<td>R1-endo</td>
<td>-0.046</td>
<td>0.049</td>
<td>19.976</td>
<td>-0.671</td>
<td>33.544 (21.67)*</td>
<td>13.916 (1.85)*</td>
<td>21.160</td>
<td>21.238</td>
<td>1.241E+08</td>
<td>8.003E-04</td>
<td>1.550E+11</td>
</tr>
<tr>
<td>R1-exo</td>
<td>-0.045</td>
<td>-0.049</td>
<td>20.493</td>
<td>-1.563</td>
<td>34.031 (22.23)*</td>
<td>11.960 (-0.02)*</td>
<td>21.677</td>
<td>23.649</td>
<td>4.919E+07</td>
<td>1.445E-05</td>
<td>3.405E+12</td>
</tr>
<tr>
<td>R2-endo</td>
<td>-0.045</td>
<td>-0.049</td>
<td>1.794</td>
<td>-25.849</td>
<td>29.258 (22.23)*</td>
<td>-11.136</td>
<td>16.978</td>
<td>42.235</td>
<td>1.214E+11</td>
<td>2.160E-19</td>
<td>5.622E+29</td>
</tr>
</tbody>
</table>

*a*change in entropy were in units of kcal/(mol*K). *b*Enthalpy change, free energy change, and activation energy were in units of kcal/mol. *c*k was expressed in s⁻¹. *d*k was expressed in s⁻¹. *e*The equilibrium constant has no units. Literature values *f*
enthalpy and free energy, this discrepancy is insignificant and could even be attributed to approximation error on Gaussian.

This result is not unexpected because all the reactions are essentially the same—a six-member ring is formed in addition to a double bond and two double bonds are destroyed. The formation of the ring is mainly responsible for net decrease in entropy. This reduces the amount of translational states available to the molecule, thereby lower the final product’s entropy. The effect would disfavor formation of any products observed in the reactions. Due to homogenous results, it was concluded entropy could not be a strong driving force for any of the reactions. It is impossible to differentiate any of the four reactions based on entropy analysis.

**Enthalpy**

The four enthalpy curves show more stark differences. It is immediately clear that all the reactions are exothermic (Figure 3B, Table 1). However, reaction 2 is far more exothermic than reaction 1. The formation of *exo*-5 in reaction 2 is 21.836 kcal/mol more exothermic than the formation of *exo*-3 in reaction 1. Similarly, the formation of *endo*-5 in reaction 2 is 25.178 kcal/mol more exothermic than the formation of *endo*-3 in reaction 1. This intriguing result can be associated with furan’s aromaticity. The greater stability afforded to furan by this aromaticity in turn lowers the energy and, thus, enthalpy of the reactants without affecting the products. Hence, the net exothermicity of the reaction is closer to 0 than that of reaction 2 since 1,3-cyclohexadiene does not offer this property.

Molecularly, both reactions exhibit exothermic character because of the creation of two σ bonds at the expense of 2 π bonds. π-bonds are known to be higher energy that σ bonds. Thus, the energy difference from this conversion is released, resulting in an exothermic reaction.

Additionally, the enthalpies of activations for the endo pathways were less than that for the exo pathways (Table 1). The differences were more pronounced in reaction 2 than in reaction 1. The difference between the two pathways in reaction 1 was 0.517 kcal/mol, while the

![Figure 4: Possible steric interactions in the final product of reaction 2. The orange area points to possible steric interactions in A) *exo*-5 and B) *endo*-5. As shown, the steric crowding appears to be more pronounced in the in *exo*-5 as opposed to *endo*-5. Though, this theory is questionable because the areas of interaction in *exo*-5 are still fairly far apart.](image-url)
difference between the two pathways for reaction 2 was 2.829 kcal/mol. This represents nearly a 5.472 fold difference. As expected, the formation of exo-3 was more exothermic than the formation of endo-3 by 1.892 kcal/mol. This, though, did not carry over into reaction 2. The formation of endo-5 was more exothermic than the formation of exo-5 by 1.450 kcal/mol. At first, this seems incorrect. According to the general exo product characteristics, the exo product should be less sterically hindered compared to the endo product and, thus, lower energy, resulting in a greater net loss in enthalpy. However, a relook at the exo-5 structure reveals that it may be more sterically hindered than the endo-5 (Figure 4). Hence, it is likely, from analyzing the enthalpy data, that the endo-5 product is the kinetic product and the thermodynamic product in which case only the endo-5 product should be observed. It is also likely, though, that this may only be due inherent inaccuracies of the DFT-B3LYP/6-31G approximation. Nevertheless, the formation of endo 5 should be kinetically favored due to its lower enthalpy of activation.

Product Distribution

From this data alone, it is difficult to quantify what the long-term expected distribution of endo and exo product is. This can be done by using a Boltzmann distribution (equation 2).

$$\frac{N_{exo}}{N_{endo}} = \frac{e^{\frac{E_{exo}}{kT}}}{e^{\frac{E_{exo}}{kT}} + e^{\frac{E_{endo}}{kT}}}$$

Equation 2 assumes that the exo product is lower in energy compared to the endo product. This is normally the case. If, however, the computational results for reaction 2 are correct, the exo and endo would be flipped. Making the general assumption that the exo product is lower in energy, the equation can be simplified by taking all energies to be relative and setting the lower energy level equal to 0 (equation 3).

$$\frac{N_{exo}}{N_{endo}} = \frac{1}{1 + e^{\frac{E_{endo}}{kT}}}$$

All the inputs for equation 3, though, are not available. It is not possible to obtain solvent interactions with the molecule because all calculations are in the gas phase. While this may seem insignificant, they are needed to obtain an accurate $E_{endo}$, the complete energy profile of this particular product.

Free Energy and Solvent Models

The free energy data highlights the importance of solvent models. Though the free energy curves shows trends analogous to the enthalpy curves, the free energy of reaction does show something unusual. In the gas phase, free energy data shows that reaction 2 is spontaneous in the forward direction while reaction 1 is not (Figure 3C, Table 1). This positive $\Delta_f G^o$ is the result of the decrease in entropy, making it impossible for the reaction to occur in the gas phase. It is not surprising that the actual reaction is run in methylene chloride solvent. Even then, the gas phase data does hint at reaction 1’s susceptibility to the reverse reaction.
Solvent models were not added since they would add additional variables to the reaction. Instead, running the gas phase reaction would provide a general and accurate understanding onto which a solvent model could be added on later. It has been shown, computationally, that adding a benzene solvent model results in a 2.08 kcal/mol decrease in the free energy of reaction for formation of endo-3 and a 2.78 kcal/mol decrease in that for formation of exo-3. While this is not enough to produce a net negative change in the free energy of reaction, it still shows the potential for a solvent to lower the free energy of reaction. In the literature, the reaction was actually run in methylene chloride. This fairly nonpolar solvent may have a significant effect on the ΔrG° of the reaction, making it feasible. All other observations indicated the free energy curves showed analogous trends to the enthalpy curves. Future work would include running the reactions in solvent models in order to gather more accurate free energy predictions and a distribution for the endo and exo products of a reaction.

These unusual predictions in the free energy of the reaction can also be the result of a small basis set and the use of the DFT-B3LYP method. As shown by literature data (Table 1), the free energy of reaction for reaction 1, while still positive for the endo adduct, is much closer to 0. This amounts to a net differences in the free energy of reactions close to 12.07 kcal/mol for the endo pathway and 11.94 kcal/mol for the exo pathway. The free energy of activations also display large differences with discrepancies of 11.87 kcal/mol for the endo pathway and 14.80 kcal/mol for the exo pathway. These large inconsistencies indicate the need for future work involving a larger basis set and a better method. Literature suggests the MP2/6-311+G(d,p) level with frequency calculations at the CBS-QB3 level is optimal for computations involving the Diels-Alder reaction.

**Activation Energy, Rate Constants, and Equilibrium Constants**

Using these datasets, it is possible to obtain rate constants and equilibrium constants. This is done by using the Arrhenius equation and substituting in the Arrhenius preexponential factor and activation energy. Since the Arrhenius preexponential factor is a function of ΔrS°, it acts more as a correction factor than a differentiator since the entropies of activation are essentially the same across all the examined reactions. For this reason, a discussion of the behavior of the activation energy is more necessary.

It was found that the activation energy of the exo transition state is greater than that of the endo transition state by 0.517 kcal/mol and 2.829 kcal/mol for reaction 1 and 2 respectively. These differences in activation energy correspond with the differences previously mentioned in the enthalpy of activation.

It is striking that the activation energies of the forward pathways for reaction 1 are comparable to that of the reverse pathways (Table 1). The activation energies of the retro-Diels-Alder for the endo and exo pathways are 21.238 kcal/mol and 23.649 kcal/mol respectively. This corresponds to only a 0.078 kcal/mol and 1.972 kcal/mol difference in activation energies between the forward and reverse directions for the endo and exo pathways respectively. The similarity in activation energies between the reactants and products again suggest the reaction to be highly reversible. This data predicts that the endo pathway is more reversible than the exo pathway. Therefore in the long run, it is possible that there will be an accumulation of exo-3.

In contrast, the activation energies of the forward reactions for reaction 2 show much lower activation barriers compared the reverse reaction (Table 1). Additionally, the reverse reaction for both pathways has activation energies more than twice that of the forward reaction.
The difference between activation energies of the forward and reverse direction for the endo and exo pathways is 25.257 kcal/mol and 23.807 kcal/mol respectively. As a result of this, it is possible to speculate that reaction 2 may have a much lower reversibility than reaction 1.

The calculated rate constants and equilibrium constants largely quantified what was already predicted from the entropy, enthalpy, and free energy curves. Nevertheless, they added a very useful quantitative perspective to the relationship between these two reactions and their two pathways (Table 1).

The formation of the endo-5 in reaction 2 has a rate constant 978.773 times greater than that of the formation of endo-3 for reaction 1. This can be attributed to the height of the activation barrier. The endo pathway for reaction 1 has a reaction barrier 4.182 kcal/mol higher than that of reaction 2.

The two exo reactions have more similar rate constants, but nevertheless highlight how fast reaction 2 proceeds compared to reaction 1 (Table 1). In this case, the formation of exo-5 for reaction 2 has a rate constant only 17.578 times greater than that for the formation of exo-3 in reaction 1. The reaction barrier for reaction 1 is only 1.870 kcal/mol greater than that of reaction 2. These differences indeed highlight the stunning effect of even a small decrease in the activation barrier of a reaction.

In both cases, the aromaticity of furan is likely the main reason why the activation barrier for both pathways in reaction 1 is greater than that for the two pathways in reaction 2. Similar to its effect on the enthalpy of the reactants relative to the products, the aromaticity gives stability to the reactants, lowering their energy, while not affecting the reactants. This in turn, raises the activation energy.

The rate data also shows the difference between the reverse reactions (Table 1). The decomposition of endo-3 in reaction 1 is 3.705 \times 10^{15} times faster than the decomposition of endo-5 in reaction 2. The decomposition of exo-3 in reaction 1 is 1.041 \times 10^{15} times faster than the decomposition of exo-5 in reaction 2. This is all to say that the retro-Diels-Alder reaction essentially does not happen in reaction 2. However, reversal to 1 and 2 from endo-3 or exo-3 in reaction 1 is by no means fast. The equilibrium constant heavily favors the forward direction. However, the equilibrium constant for the exo pathway of reaction 1 is nearly 21.959 times that of the endo pathway. The rate constant for the reverse endo pathway of reaction 1 is also 55.388 times that of the reverse exo pathway. In short, the endo pathway is much more reversible than the exo pathway. Though the endo pathway has a rate constant 2.522 times that of the exo pathway, due to the endo pathway’s significantly greater penchant for reversibility, exo-3 will most likely result in the long run.

Taken together, a careful look at the thermodynamic and kinetic profile of these two reactions show the expected long-term formation of the endo product for reaction 1 and the definite formation of the endo product for reaction 2 with very little observable exo product. In this case, reaction 1 is predicted to violate Alder and Stein’s endo rule.

*Temperature effects on these calculations*

With the understanding of the thermodynamic and kinetic behavior of these two reactions at STP, an effort was made to test a change in temperature. The same computational methods were applied with the keyword “temperature =313” to change the reaction temperature from 278.15K to 313K.
Table 2: A comprehensive table of thermodynamic and kinetic parameters for the endo and exo pathways of reaction 1 and 2 at 313K.

<table>
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<th>$\Delta_\text{S} \text{ b}$</th>
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<th>$\Delta_\text{H} \text{ b}$</th>
<th>$\Delta_\text{G} \text{ a}$</th>
<th>$\Delta_\text{G} \text{ b}$</th>
<th>$E_\text{a}^f$</th>
<th>$E_\text{a}^r$</th>
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<th>$k_\text{r}$</th>
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<tr>
<td>R1-endo</td>
<td>-0.045</td>
<td>-0.049</td>
<td>19.987</td>
<td>-0.671</td>
<td>34.223</td>
<td>14.628</td>
<td>21.172</td>
<td>21.250</td>
<td>1.200E+08</td>
<td>7.922E-04</td>
<td>1.515E+11</td>
</tr>
<tr>
<td>R1-exo</td>
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<td>-0.049</td>
<td>20.502</td>
<td>-2.569</td>
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<td>12.683</td>
<td>21.686</td>
<td>23.663</td>
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<td>1.372E-05</td>
<td>3.496E+12</td>
</tr>
<tr>
<td>R2-endo</td>
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<td>-0.049</td>
<td>15.798</td>
<td>-25.873</td>
<td>29.925</td>
<td>-10.407</td>
<td>16.982</td>
<td>42.264</td>
<td>1.190E+11</td>
<td>1.962E-19</td>
<td>6.065E+29</td>
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<tr>
<td>R2-exo</td>
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<td>-0.050</td>
<td>18.628</td>
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<td>32.651</td>
<td>-8.801</td>
<td>19.812</td>
<td>43.644</td>
<td>8.472E+08</td>
<td>1.258E-20</td>
<td>6.736E+28</td>
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<table>
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<tr>
<th></th>
<th>$\Delta_\text{S} \text{ a}$</th>
<th>$\Delta_\text{S} \text{ b}$</th>
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<th>$\Delta_\text{H} \text{ b}$</th>
<th>$\Delta_\text{G} \text{ a}$</th>
<th>$\Delta_\text{G} \text{ b}$</th>
<th>$\Delta_\text{E}^f$</th>
<th>$\Delta_\text{E}^r$</th>
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<th>$\Delta k_\text{r}$</th>
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<tr>
<td>R1-endo</td>
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<td>0.667</td>
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<td>0.029</td>
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<td>-1.980E-20</td>
<td>4.430E+28</td>
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<tr>
<td>R2-exo</td>
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<td>0</td>
<td>0.005</td>
<td>-0.025</td>
<td>0.662</td>
<td>0.738</td>
<td>0.005</td>
<td>0.03</td>
<td>-1.750E+07</td>
<td>-1.300E-21</td>
<td>5.070E+27</td>
</tr>
</tbody>
</table>

*change in entropy were in units of kcal/(mol*K).  Enthalpy change, free energy change, and activation energy were in units of kcal/mol.  $k_\text{f}$ was expressed in s$^{-1}$M$^{-1}$.  $k_\text{r}$ was expressed in s$^{-1}$.  The equilibrium constant has no units.

Small, but important changes in key thermodynamic and kinetic parameters were observed (Table 2). The rates of forward and reverse reaction were computed to be slower, the result of higher activation barriers for the forward and reverse reactions. Also, with the exception of the endo pathway for reaction 1, the equilibrium constant for all reactions appeared to grow. The factors least affected by this temperature change were entropy and enthalpy. These parameters were constant compared to the free energy change.

As a result of the higher temperature, the free energy of activation and reaction both increased (Table 2). Mathematically, this is expected. According to the relationship of free energy with entropy and enthalpy, the entropy term’s effect will be magnified at increasing temperatures. Since the reaction involves an entropy loss and enthalpy gain, this would result in a total net gain in free energy. The inverse is also true. With decreasing temperatures, the free energy of activation and reaction will go down. Experimentally, an ice bath may make for more favorable conditions.

Experimental Observations

The two reactions were run and stored for a week, after which the melting point of the product was taken. It was observed that the furan-maleic anhydride adduct had an average melting point extremely similar to the literature melting point of the exo product$^{12}$ (Table 3). In contrast, the average melting point of the 1,3-cyclohexadiene-maleic anhydride adduct was extremely similar to the literature melting point for the endo product$^{12}$ (Table 3). These results confirmed the theoretical model of the reaction pathway.

Table 3: Final Adduct Melting Point Measurements

<table>
<thead>
<tr>
<th></th>
<th>Furan Adduct*</th>
<th>1,3 Cyclohexadiene Adduct*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed</td>
<td>113.9 ± 0.7</td>
<td>147.7 ± 0.7</td>
</tr>
<tr>
<td>Expected (Exo)</td>
<td>114$^{12}$</td>
<td>157-158$^{12}$</td>
</tr>
<tr>
<td>Expected (Endo)</td>
<td>80-81$^{12}$</td>
<td>147$^{12}$</td>
</tr>
</tbody>
</table>

*the average melting point in °C
Taking the melting point of the furan-maleic anhydride adduct resulted in the adduct melting and then shooting up the test tube. This effect is likely due to the retro-Diels-Alder reaction. As a result of the high temperature, furan (bp=31.3 °C, 304.45K) likely boiled away. This effect was not observed upon taking the melting point of the 1,3-cyclohexadiene-maleic anhydride adduct, though 1,3-cyclohexadiene has a boiling point of 80°C (353K), well below the melting point of the adduct. This likely indicates that the retro-Diels-Alder reaction did not take place. It highlights the high activation barrier of the retro-Diels-Alder reaction for the 1,3-cyclohexadiene-maleic anhydride adduct compared to that for the furan-maleic anhydride adduct. This, again, is in line with the predictions of the thermodynamic and kinetic data.

**Orbital Picture**

The thermodynamic and kinetic picture, though, does not fully explain why the endo preference is observed. Counter-intuitively, the endo pathway actually proceeds through a more sterically hindered transition state due to proposed secondary orbital interactions (SOI)\(^{13–15}\). These interactions are specific to pericyclic reactions\(^{17}\) and help stabilize only the endo transition state for the reaction, as shown in the figure.

**Figure 5: Orbital interactions and carbon-carbon lengths.** The primary orbital interactions (blue) and secondary orbital interactions (orange) in the transition states for A) reaction 1 and B) reaction 2 for the endo pathway. The green and red indicate orbitals of differing wave function sign. C) The carbon-carbon length in the transition state for both reactions and pathways. The length is in angstroms and the primary orbital interactions are in blue as opposed to black. These interactions are where the sigma bond will form. The secondary orbital interactions could possibly stabilize the transition state, though are between two relatively far away carbon atoms.
state. They are identified as interactions between the orbitals involved in the reorganization of the $\pi$ system that do not ultimately form $\sigma$ bonds$^{17}$.

Recently, this theory has come under scrutiny. Literature shows that the carbons atoms involved in secondary orbital interactions are in fact extremely far away from each other$^{16-18}$. By some estimates$^{18}$, the distances of the carbons involved in secondary orbital interaction (SOI) in the *endo* pathway of reaction 1 are 2.962 Å away (Figure 5). As shown by Figure 5, reaction 2 also displays a similar problem. An in-depth study of the reaction attributed the *endo* preference to dispersion interactions which operate through $\pi-\pi$ contacts and solvent effects because of there was no evidence for charge transfer at the transition state$^{16}$. This data was obtained by looking at Mulliken charge transfer. This method is highly dependent on the basis set and often considered to be inaccurate, though useful for identifying trends. Though the paper concluded that there was no evidence for charge transfer, their data indicated an imbalance of .01e, hinting at the possibility of albeit on an extremely small scale. The basis set used is also too small to provide accurate measurements. The use of second-order perturbation theory demonstrated their existence, though indicating the small magnitude of these interactions$^{18}$. Similarly, as shown by the free energy and the enthalpy data, even if SOI’s were responsible for the *endo* preference, the added stabilization is extremely small (Figure 3B&C, Table 1).

This small impact fails to explain the enormous *endo* preference seen in reaction 2 (Table 1). Recently, literature has shown that SOI motivating the *endo* product does appear to in fact exist, theoretically, in a similar reaction involving cyclopentene and cyclopentadiene$^{11}$. This result, however, is not easily transferrable reaction 2 due to the differing stereochemistry of cyclopentadiene and 1,3-cyclohexadiene. Future study will concern itself with the use of a theoretical nuclear-independent chemical shifts (NICS) calculation on both reactions. It can be assumed that if NICS calculations demonstrate aromaticity, and thus electron delocalization, in the transition state, there exists the possibility for SOI. Electron delocalization would only happen if SOI was involved in the transition state and not be the result of dispersion or steric effects$^{11}$. In addition, the application of second order perturbation theory$^{28}$ on data obtained from a natural bond orbital analysis$^{18}$ would further clarify results. Nevertheless, it is tempting to speculate that the *endo* and *exo* selectivity for a reaction may be the combination of SOI, steric, electrostatic, and dispersion forces acting in concert.

**Conclusion**

A detailed look at the thermodynamic, kinetic, and molecular profile of these two model Diels-Alder reactions not only highlight the reaction’s complexity but also its elegance. Though from these computations, it is clear that aromaticity and energy loss are important factors for the reaction, the molecular players in *endo* and *exo* selectivity remain the subject of debate. Future research into these factors may yield novel tools that could revolutionize the way this reaction is used in organic synthesis.
References and Acknowledgements

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(9) Alder, K.; Stein, G. Justus Liebig’s Annalen der Chemie 1934, 514, 1–33.
(12) Henry Gingrich; Miles Pickering In The Organic Puzzle Book; 2011; pp. 95–98.
The Determinants of *Endo* and *Exo* Selectivity in Diels-Alder Reactions of Maleic Anhydride: A Theoretical Study

SUPPLEMENTAL INFORMATION
Experimental Method

All experiments were done in accordance with the literature. Final melting point data was the average of two sets of numbers.

<table>
<thead>
<tr>
<th></th>
<th>Furan Adduct*</th>
<th>1,3 Cyclohexadiene Adduct*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Run 1</td>
<td>111.4 ± 0.5</td>
<td>148.9 ± 0.5</td>
</tr>
<tr>
<td>Run 2</td>
<td>116.4 ± 0.5</td>
<td>146.4 ± 0.5</td>
</tr>
<tr>
<td>Average</td>
<td>113.9 ± 0.7</td>
<td>147.7 ± 0.7</td>
</tr>
</tbody>
</table>

*in °C

Computational Background

All calculations were performed in Gaussian09 using Gaussview 5 in the gas phase. Frequency results verified the validity of the optimization. The observation of a single imaginary frequency confirmed transition state computations. The observation of no imaginary frequencies confirmed all other computations.

The DFT-B3LYP method is a hybrid DFT-SCF method. It employs the use of functionals as a way of relating electron density with energy, thereby improving upon the Hartree-Fock (HF) model which does not consider electron interaction. It also adds on Becke’s three parameter exchange functional (B3) and Lee, Yang, and Parr correlation functional (LYP). Doing so enables the method to be only slightly more computationally intensive than HF while providing a vastly more accurate data.

The 6-31G basis set is a split-valence basis set. The core 1s orbital is represented by 1 set of functions containing 6 Gaussians. The valence orbitals are represented by two sets of functions. One set contains 3 Gaussians and the other set contains only 1 Gaussian. Extra functions (d, p, and diffuse functions) were not added onto 2nd row elements or H.

The consequence of these tradeoffs is data that will likely only be useful in providing trends for study. The actual values may have significant errors associated with them.

Computational Method

Maleic Anhydride-Furan Reaction

The maleic-anhydride-furan adduct was constructed through the use of two cyclopentadiene model molecules in the builder interface. The substituents on these two rings were changed to match that of maleic anhydride and furan. Then, using the “Modify Bond” option in the builder menu, the proper bonds were selected and changed to single or double bonds.

In order to draw the endo adduct, the maleic anhydride was positioned with the oxygens directly under the furan ring. To create the exo adduct, the maleic anhydride was positioned with the oxygens away from the furan ring. Using “Modify Bond” in the builder menu again, two bonds were drawn between these two rings at where the Diels Alder reaction would form bonds and all bond types were checked to make sure they were representative of the adduct.
“Edit=>Clean” option was finally selected to obtain a rough approximation for the resulting adduct.

This product was now optimized. The calculation menu can be accessed by going to “Calculate=>Gaussian Calculation Setup.” Under “Job-Type,” “Opt+Freq” was selected from the pull-down menu. It was checked that the setup optimized the product to a minimum. Under “Method,” the DFT-B3LYP method was selected with default spin. The 6-31G basis set was used. There was no charge and the molecule was a singlet. Finally, under “Link 0,” the edit interface was selected. The following parameters were inputed: %mem=6GB and %nproc=2. These parameters mean this calculation will use up to 6 gigabytes of ram and 2 processors. It is recommended that for the calculation, 75% of the computer’s ram be used. The number of processors used should be based on the computer’s specifications. For these calculations, a 2010 MacBook with a 2.4 GHz Intel Core 2 Duo processor and 8 GB 1067 MHz DDR3 of memory.

After all calculation parameters have been specified, the job was submitted to Gaussian09.

After the calculation was complete, the log file for the product was opened. The existence of no imaginary frequencies confirmed the product was optimized correctly. The optimized product was then copied into a new screen for the optimization of the reactants. Using the “Modify Bond” option in the Builder Menu, bonds between maleic anhydride and furan were removed. The molecules were then moved far apart from each other by selecting the two atoms that had a bond between them formed by the Diels-Alder Reaction. The molecule on the furan was selected first and the molecule on the maleic anhydride selected second. Under the “displacement” option, atom 1 was fixed. Atom 2 had its group translated. This was done by moving the slider bar to position the molecules as far away as possible. The same actions were performed for the second set of atoms as well with the molecules being selected in the same order. The “Modify Bond” option was then used to change the bonds of maleic anhydride and furan to their desired bond configurations. Following this, the “Clean” command was applied to the set of reactants.

Before optimizing the reactants, one more step was done to ensure the reactants would stay separate, but yet close enough to be reactive. Under the “Edit” menu, the “Redundant Coordinates Editor” was selected. The two sets of atoms in which a new bond would form were added by selecting add, clicking the two atoms, selecting add again, and clicking on the next set of atoms. In both cases, the unidentified preference was changed to “Bond” and the option to “Freeze Bond” was selected.

After the appropriate coordinates were frozen, the same calculation setup as the products was performed. At this point, the optimized product and reactants for the reaction were used to optimize the transition state. The optimization of the transition employed the QST3 method, which optimized the predicted transition state in relation to the products and reactants. The predicted transition state was drawn starting with the product. This step involved the same procedure as the drawing the reactants. However, the distance between the two reactants was set to approximately 2Å. The redundant coordinate editor was not used.

The reactants, product, and transition state were pasted onto the same window with each set being added to the molecule group. All three states were viewed in the same window using the “view both” toggle on the window toolbar. It was verified that the reactants, product, and transition state appeared in pane 1, 2, and 3 respectively.
The transition state now needs to be optimized. This was done by going to the “Gaussian Calculation Setup” and selecting “Opt+Freq” again. Instead of performing optimizing to a “minimum,” the option “TS (QST3)” was selected. It was also verified that geometry 3 was used for the transition state (TS) guess. All other specifications were the same as the optimization for the products and reactants. A valid transition state should contain one imaginary frequency.

Carbon to carbon distance data was then gathered using the “inquire” tool located on the builder palette.

**Maleic Anhydride-1,3-cyclohexadiene Reaction**

The procedure followed the same approach as the calculations for the maleic anhydride and furan reaction. 1,3-cyclohexadiene was substituted in place of furan and 3GB of RAM was specified instead of 6GB. This reaction was run on a 2010 MacBook Pro with a 2.66 GHz Intel Core Duo processor and 4 GB of 1067 MHz DDR3 memory.

**Molecular Analysis**

Atom-atom distances were measured using the “inquiry” tool in the builder interface. These were recorded to determine the validity for secondary orbital interaction (SOI).

Molecular orbital diagrams were generated using “Surfaces and Contours” tool located in “Results”=>”Surfaces/Contours.” This result was only available from the .chk file. A cube was first generated by selecting “new cube” under “cube actions.”

**Thermochemistry Data Analysis**

Before all the thermochemical data could be analyzed, it is important to obtain separate optimizations of the reactants. Simply extracting information from the .log file containing the optimization of both reactants together may yield inaccurate results.

Thermochemistry data was obtained and analyzed following literature methods\(^\text{32}\). The data was obtained from the .log file in the “Thermochemistry” section. This .log file data was opened by right-clicking and selecting “Results”=>”View File.” The following output is an example of the type of data recorded into Excel:

```
Zero-point correction= 0.126461 (Hartree/Particle)
Thermal correction to Energy= 0.137422
Thermal correction to Enthalpy= 0.138365
Thermal correction to Gibbs Free Energy= 0.085898
Sum of electronic and zero-point Energies= -608.993724
Sum of electronic and thermal Energies= -608.972763
Sum of electronic and thermal Enthalpies= -608.971819
Sum of electronic and thermal Free Energies= -609.824287
```

The most relevant outputs for paper was the sum of the electronic and thermal enthalpies \((\epsilon_0 + H_{corr})\) and the sum of the electronic and thermal free energies \((\epsilon_0 + G_{corr})\).
First, Gibbs free energy of reaction $\Delta_r G^\circ$ and enthalpy of reaction $\Delta_r H^\circ$ was calculated. The sign of $\Delta_r G^\circ$ tells whether the reaction is spontaneous ($\Delta_r G^\circ > 0$) or not ($\Delta_r G^\circ < 0$). The sign of $\Delta_r H^\circ$ highlights whether the reaction is exothermic ($\Delta_r H^\circ > 0$) or endothermic ($\Delta_r H^\circ < 0$).

\[
\Delta_r G^\circ = \sum (\varepsilon_0 + G_{corr})_{products} - \sum (\varepsilon_0 + G_{corr})_{reactants} \quad \text{(S1)}
\]

\[
\Delta_r H^\circ = \sum (\varepsilon_0 + H_{corr})_{products} - \sum (\varepsilon_0 + H_{corr})_{reactants} \quad \text{(S2)}
\]

This, however, does not give any information about the kinetics of the reaction. To determine that, the enthalpy of activation $\Delta^\ddagger H^\circ$ and free energy of activation $\Delta^\ddagger G^\circ$ need to be calculated.

\[
\Delta^\ddagger G^\circ = \sum (\varepsilon_0 + G_{corr})_{transition\ state} - \sum (\varepsilon_0 + G_{corr})_{reactants} \quad \text{(S3)}
\]

\[
\Delta^\ddagger H^\circ = \sum (\varepsilon_0 + H_{corr})_{transition\ state} - \sum (\varepsilon_0 + H_{corr})_{reactants} \quad \text{(S4)}
\]

Using these quantities, the entropy of activation $\Delta^\ddagger S^\circ$ and entropy of reaction $\Delta_r S^\circ$ can be calculated.

\[
\Delta G = \Delta H - T\Delta S \quad \text{(S5)}
\]

\[
\Delta^\ddagger S^\circ = \frac{\Delta^\ddagger H^\circ - \Delta^\ddagger G^\circ}{T} \quad \text{(S6)}
\]

\[
\Delta_r S^\circ = \frac{\Delta_r H^\circ - \Delta_r G^\circ}{T} \quad \text{(S7)}
\]

...where $T=298.15K$

With these quantities, the Arrhenius activation energy ($E_a$) and preexponential factor ($A$) can be calculated.

\[
\text{Gas, uni} \quad E_a = \Delta^\ddagger H^\circ + RT \quad A = \frac{e k_B T}{h} e^{\Delta^\ddagger S^\circ / R} \quad \text{(S8)}
\]

\[
\text{Gas, bi} \quad E_a = \Delta^\ddagger H^\circ + 2RT \quad A = \frac{e^2 k_B T}{h} e^{\Delta^\ddagger S^\circ / R} \quad \text{(S9)}
\]

...in which the forward-Diels-Alder reaction is a bimolecular gas phase reaction and the retro-Diels-Alder reaction is a unimolecular gas phase reaction. $k_B$, $h$, and $R$ are the Botzman constant, Planck’s constant, and the universal gas constant respectively.

Finally, using these quantities in the Arrhenius expression, it is possible to calculate the rate constant of a reaction and equilibrium constant for the forward and reverse reactions:
\[ k = A e^{-\frac{E_a}{RT}} \]  
\[ K_{eq} = \frac{k_f}{k_r} \]  

…where \( k_f \) is the forward reaction rate constant and \( k_r \) is the reverse reaction rate constant. It is important to note that the forward and reverse reaction rate constants are calculated using different activation energies and have different enthalpies and entropies of activation.

These calculations were done for the endo and exo reactions of maleic anhydride with furan and maleic anhydride with 1,3-cyclohexadiene.

**Analysis at \( T = 313K \)**

All procedure remained the same. However, all calculations in *Gaussian09* used the keyword temperature=313. Additionally, when analyzing the data, the value of temperature was taken to be 313K instead of 298.15K.

**Key Errors**

As mentioned, the use of the DFT-B3LYP method and 6-31G basis set may not produce the most optimal results. Literature has shown that density functional methods at the B3LYP/6-311G(d,p), a much larger basis set than what was used, produced data that deviated significantly from experimental values in the gas phase and in solvent models for acetonitrile and chlorobenzene\(^{27}\). This is primarily the case because of the heteroatoms also involved in the distribution of electron charge in the two model Diels-Alder reactions studied in this paper\(^{33}\).

There were also warnings indicating various degrees of freedom may cause errors in results and warnings regarding the assumption of classical behavior for rotation. These keywords freq=hinderedrotor, opt=tight, and opt=verytight were used to try and rectify these warnings. The final results though did not yield data that was different than that not obtained by using these key words. These errors indicate that thermodynamic and kinetic values may be inaccurate, but the trends should still hold.