

## Application of the G3(MP2)-CEP theory in understanding Diels-Alder mechanism

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### INTRODUCTION

Even 80 years after the formulation of the “endo rule” proposed by Alder and Stein in 1934,<sup>1</sup> the factors controlling the formation of endo product in [4+2] cycloaddition reactions are still not completely understood.<sup>2</sup> In the context of organic synthetic chemistry, the Diels–Alder reaction is among the most powerful and well-known mainly due to the facility of generating two carbon-carbon bonds simultaneously.<sup>3</sup>

There are at least three points in an attempt to explain the preference that leads to the formation of a given product in this type of reaction. The first one is the Secondary Orbital Interactions (SOI) proposed by Hoffmann and Woodward<sup>4</sup> to rationalize the empirical endo rule formulated by Alder and Stein, as previously mentioned. Arrieta and Cossío<sup>5</sup> studying the classical Diels-Alder reaction between cyclopentadiene (CP) and maleic anhydride (MA), claim that SOI do exist and are responsible for at least an important part of the observed stereo control.

An opposite tendency is defended by García, Mayoral and Salvatella<sup>6</sup> which justify that the SOI concept was based on the assumption that closed-shell repulsions were identical in endo and exo approximations. Therefore, the SOI concept is unnecessary and should be abandoned by chemists as a general explanation for the endo preference in Diels-Alder reactions. The study by Ogawa and Fujimoto based on the reaction between maleic anhydride and butadiene has shown that the endo preference is not due to SOIs, but to a balance of several energy terms, including electrostatic attractions and closed-shell repulsions.<sup>6,7</sup> As a logical conclusion, the endo preference of the cyclopentadiene and maleic anhydride reaction

should be essentially attributed to the steric repulsion induced by the methylene group in the exo approach, although other interaction mechanisms (such as dispersion forces) may also play a role.<sup>6,7</sup> Fernández and Bickelhaupt have also confirmed that neither the orbital interactions nor the total interaction between the deformed reactants contributes to the endo selectivity. They believe that the selectivity is mainly caused by an unfavorable steric arrangement in the transition-state region of the exo pathway which translates into a more destabilizing activation strain.<sup>1</sup>

Another relevant question is the solvent effect that seems to have certain influence in some properties depending on the system. The classical work of Cativiela *et al.*<sup>8</sup> illustrates examples in which the polarity of the solvent changes the selectivity endo/exo in Diels-Alder reactions. However, overall donor properties of the solvent are not important, although in some reactions a solvent with high donation ability may reduce the reaction rate. On the other hand, Tuvi-Arad and Avnir<sup>9</sup> studying the classical reaction of [4 + 2] cycloaddition of (E,E)-1,4-dimethoxy-1,3-butadiene (DMB) with tetracyanoethylene (TCNE), show that the reactivity increases with the polarity of the solvent used.

Independent of the hypothesis being analyzed, the alliance between computation and experimental results has been increasingly used with the goal to provide subsidies for the discussion on the clarification of structural and/or electronic properties of various types of reactions, including the cycloaddition reactions [4+2] as is the case of Diels-Alder reactions.

Significant advances in reducing the computational cost while preserving the accuracy

was recently developed by Pereira *et al.*<sup>10,11</sup> combining a Compact Effective Pseudopotential (CEP) of Stevens, Bash and Krauss<sup>12,13</sup> in the G3 theory, referred to as G3CEP theory. The method reduces the CPU time between 7 and 60% without losing quality of the results obtained. The mean absolute deviation for the method is 1.29 kcal mol<sup>-1</sup> compared to 1.16 kcal mol<sup>-1</sup> from the original all-electron method for the test set G3/05.

Rocha *et al.* similarly developed G3(MP2)//B3-CEP theory adapting the CEP in G3(MP2)//B3 theory.<sup>14</sup> The mean absolute deviation compared to the experimental data for all thermochemical results was 1.60 kcal mol<sup>-1</sup> and 1.41 kcal mol<sup>-1</sup> for theories G3(MP2)//B3-CEP and G3(MP2)//B3, respectively, with CPU time reduction between 10% and 40% using pseudopotential.

The success of these new theories developed with respect to their original all-electron methodologies, mainly due to the accuracy of results and reduced computational time, led to the implementation of CEP in the G3(MP2) reduced order theory<sup>15</sup>, which led to the G3(MP2)-CEP theory<sup>16</sup>. The objective of this study is to evaluate the performance of this new method to study the mechanism of a set of selected some Diels-Alder reactions.

## METHOD

The G3(MP2)-CEP theory is characterized by the same sequence of calculations of the G3(MP2) original theory with the replacement of core electrons by pseudopotential. The procedure for obtaining the final G3(MP2)-CEP energy is also similar and are described in the literature.<sup>16</sup> All maximums (TS, Transition State) were characterized by frequency calculation and then undergoing the IRC (Intrinsic Coordinate Reaction) procedure with the MP2/CEP-P31G(d) methodology. All calculations were carried out with Gaussian 09W software.<sup>17</sup>

Four cases were selected where the reactions have different endo/exo yields in order to evaluate the behavior of G3(MP2)-CEP theory relative to experimental results and the other calculations from the literature.

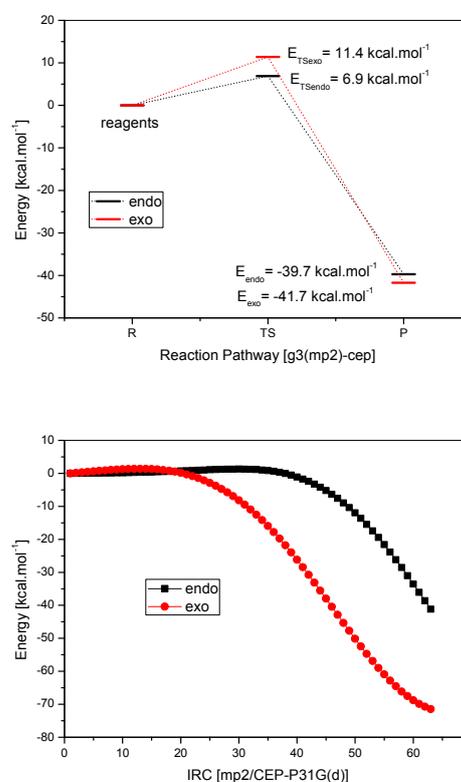
## RESULTS AND DISCUSSION

It is known that the experimental ratio of endo/exo adducts is greatly changed when the cyclopropene is replaced by cyclopentene in a

reaction with cyclopentadiene, and this was the reason for the choice of these particular mechanisms.

### Reaction 1: cyclopropene and cyclopentadiene<sup>18,19</sup>

This reaction provides an endo/exo ratio of 97:3. Figure 1 shows the energy profile calculated with: (a) G3(MP2)-CEP and (b) IRC obtained at MP2/CEP-31G(d) level indicating a kinetic preference for endo adduct, because the barrier is 4.5 kcal mol<sup>-1</sup> lower compared to the analogue which leads to the exo TS. However, the exo adduct is still the product thermodynamically more stable, which is in agreement with the endo rule proposed by Alder and Stein<sup>1</sup>.

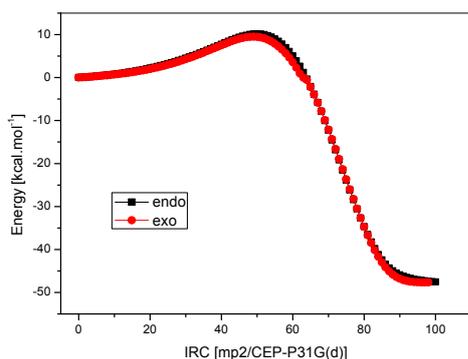
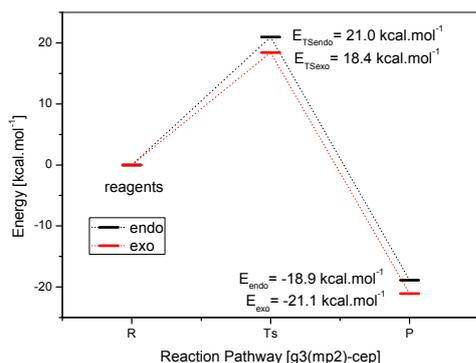


**Figure 1.** Energy profile (a) and IRC (b) for the reaction between cyclopropene and cyclopentadiene.

### Reaction 2: cyclopentene and cyclopentadiene<sup>19,20</sup>

The reaction between cyclopentene and cyclopentadiene provides a kinetic preference for the exo adduct formation. It can be seen that the difference between both barriers is approximately 2.5 kcal mol<sup>-1</sup>. The exo adduct also is the thermodynamic product. The results once again may justify the 20:80 (endo/exo) ratio found in the literature. In this case the kinetic and thermodynamic preferences point to the exo adduct (see Figure 2).

According to Liu *et al.*<sup>19</sup> the reactivity of cycloalkenes as dienophiles are controlled by distortion energies from the reactants into the transition-state geometries. The distortion energies increase from cyclopropene to cyclohexene resulting in a decrease in the Diels-Alder reactivity resulting in an enlargement of the activation barrier. Observe that the TSendo energy of the reaction 2 is practically the triple compared to reaction 1, 21.0 and 6.9 kcal mol<sup>-1</sup>, respectively.



**Figure 2.** Energy profile (a) and IRC (b) for the reaction between cyclopentene and cyclopentadiene.

On the other hand the dienes reactivities are controlled by both distortion and interaction energies. Interaction energy is the difference between the activation energy and the total energy of distortion.

The energy difference between the endo/exo stereoisomers, in reactions 1 and 2 do not exceed 2 kcal mol<sup>-1</sup>. The barrier height can justify well the experimental yield in these two situations.

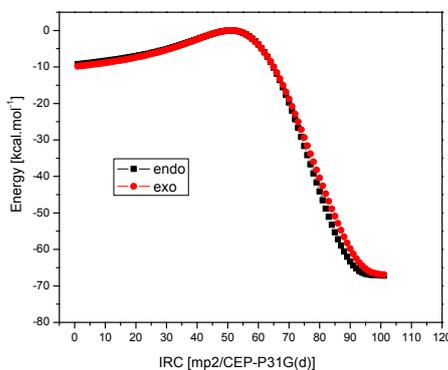
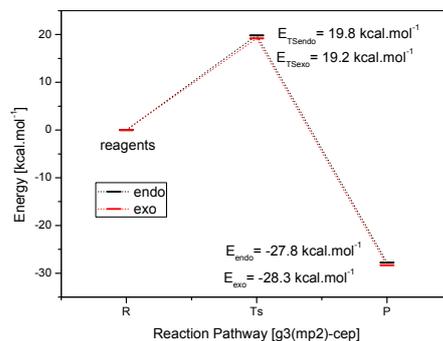
#### Reaction 3: cyclohexadiene and acrylonitrile

Tuvi-Arad and Avnir<sup>21</sup> studied the symmetry-enthalpy correlations in Diels-Alder reactions with three cyclic dienes: cyclopentadiene,

cyclohexadiene and cycloheptadiene, beyond acyclic butadiene, and three dienophiles: cyanoethylene (acrylonitrile), 1,1-dicyanoethylene and 1,1,2-tricyanoethylene. Cyanoethylene derivatives are widely studied due to their known ability to accelerate cycloaddition reactions.<sup>22</sup> In particular, cyanoethylene (acrylonitrile) is a reactive dienophile in DA reactions with cyclopentadienes, cyclohexadienes, and cycloheptadienes<sup>23</sup>. In general, the reactivity decreases as the ring size increases<sup>24</sup>.

Takakis *et al.*<sup>25</sup> showed that the reactions of cyclohexadiene and cycloheptadiene with acrylonitrile are exceptions to the Alder-Stein rules regarding the exo/endo ratio of 40:60 for cyclohexadiene (Reaction 3) and 35:65 for cycloheptadiene (Reaction 4).

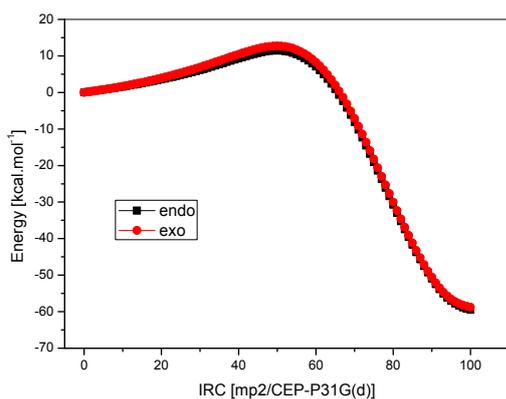
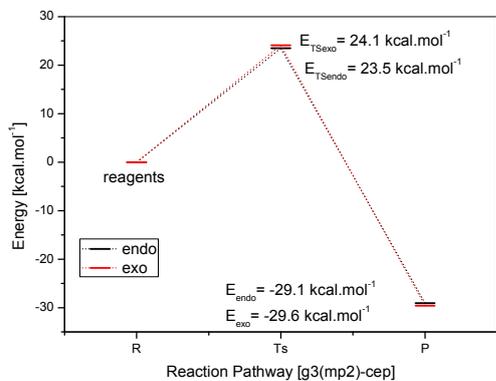
Figure 3 shows results found by G3(MP2)-CEP for the reaction between cyclohexadiene and acrylonitrile. The small energy difference between the transition states and products shows a balance between both adducts agreeing with the experimental yield.



**Figure 3.** Energy profile (a) and IRC (b) for the reaction between cyclohexadiene and acrylonitrile.

*Reaction 4: cycloheptadiene and acrylonitrile*

The small energy difference, either between TSs or products, does not allow state a high selectivity for a particular stereoisomer, agreeing therefore once again with the experimental yield 35:65 (endo/exo).



**Figure 4.** Energy profile (a) and IRC (b) for the reaction between cycloheptadiene and acrylonitrile.

It is observed in reactions 3 and 4 that the difference of energy between TSs and reaction products do not exceed 0,5 kcal mol<sup>-1</sup>. IRC profiles are also practically overlapped showing no significant difference in energy between both paths.

## CONCLUSIONS

In the Diels-Alder reactions studied one cannot reach a general conclusion to explain the preference for a particular endo/exo product from the reactants. The four mechanisms analyzed show kinetic preference for the endo stereoisomer in Reaction 1, exo in Reaction 2, and balance between both products in Reactions 3 and 4. The thermodynamic preference points to the exo

product in Reactions 1 and 2, and balance between both products in Reactions 3 and 4.

The endo rule cannot be followed in many cases, as shown in some of the reactions discussed here. Though often the experimental yield point out to high selectivity for the endo or exo product, theoretically it is not verified large differences in energy between the products formed independent of the methodology used.

The G3(MP2)-CEP theory agrees with the experimental data in all analyzed reactions, although in some cases (Reactions 3 and 4) the energy difference is very small (~0,5 kcal/mol). Worth remembering that the solvent effect has little influence in most Diels-Alder reactions. The question of SOI likewise cannot be taken into account to explain alone the selection by either adduct, as some authors claim.

The interaction and distortion energy seems the best way to explain the cases studied in this work. The G3(MP2)-CEP theory performed well in all cases tested and will be used in other situations in order to attempt to elucidate the Diels-Alder reaction yields.

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