



# An energetic analysis of the Diels-Alder endo:exo selectivity reaction by using composite methods

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## ABSTRACT

The G3(MP2)-CEP and G3(MP2) theories are applied to analyze the energetic tendency of six Diels-Alder reactions. Different energetic data were analyzed in this paper calculated by both levels of theory: energy differences, Gibbs energies, and distortion/interaction energies. The quantitative and qualitative results obtained by both theories tend to agree with the experimental data in most cases regarding the relative barrier heights, major product tendency and distortion/interaction effects, although in some cases the sufficiently small energy difference is lower than the error of the method itself. The examples studied showed that the endo rule cannot be followed in some of the reactions discussed.

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## 1. Introduction

The factors controlling the formation of the endo product in a [4 + 2] cycloaddition reaction proposed by Alder and Stein [1] are still the subject of discussion in the literature [2]. It is classified among the most important and widely studied organic reactions because of the ability to generate two carbon-carbon bonds simultaneously [3]. Brocksom et al. [4] published a review of the Diels-Alder reaction, claiming that it is a classic reaction, but there are always new perspectives with respect to new methodologies and applications in total syntheses. Two recent examples are the papers by Zeiger et al. [5] and Hoye et al. [6], where the authors analyzed the intermediates participating in the hydrogen abstraction, which may be chemically isolated allowing functionalization in unique positions of a molecule.

From the literature, at least three aspects can be identified to explain the preference for the formation of a specific product in Diels-Alder reactions. According to Hoffmann and Woodward [7] the empirical endo rule is driven by a secondary orbital interaction (SOI). Arrieta et al. [8] reached the same conclusion by studying the classical reaction between cyclopentadiene and maleic anhydride. They concluded that SOI is extremely significant and can be

pointed to as a major influence on the observed stereochemical control.

On the other hand, other researchers, e.g., Garcia et al. [9], based on the similarity of closed-shell repulsion effects in endo/exo approximations, concluded that SOI is not suitable as a conventional explanation for the preference for endo reactions. The study of the reaction between maleic anhydride and butadiene by Fujimoto and Ogawa [10] showed that different energetic factors could be considered to explain the endo preference rather than the dominant SOI effect. Electrostatic attractions and closed shell repulsions [10] could be more influential than SOI. The endo preference of the cyclopentadiene and maleic anhydride reaction can be attributed to steric repulsion induced by a methylene group in the exo approach, although other mechanisms of interaction may also play an important role [10]. A similar conclusion was stressed by Fernandez and Bickelhaupt [2], who reported that endo selectivity could not be attributed exclusively to orbital interactions or to the energetic interaction between deformed reagents.

Another important question is the solvent effect, which appears to have an influence on some properties, depending on the reactants used. The classical work by Cativiela et al. [11] illustrates examples in which the solvent polarity modifies the endo/exo selectivity in Diels-Alder reactions. However, in general, for the reactions usually studied the solvents are not important, although in some of them the reaction may proceed more slowly. On the other hand, the study by Tuvi-Arad and Avnir [12] on the reaction

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between (E,E)-1,4-dimethoxy-1,3-butadiene with tetracyanoethylene showed that the solvent polarity increases the reactivity of some compounds. Another recent work developed by Yepes et al. [13] showed that the use of different Lewis acids as catalysts may also influence the selectivity of Diels-Alder reactions.

Regardless of the aspects being analyzed, cooperation between computational methods and experiments has been increasingly used in order to provide insights for the elucidation of the structural and/or electronic effects responsible in chemical reactions such as Diels-Alder [4 + 2] cycloaddition mechanisms [14–20].

Significant progress in reducing computational costs while preserving the accuracy of the calculations has been developed recently by Pereira et al. [21,22] combining a compact effective pseudopotential (CEP) by Stevens, Bash and Krauss [23,24] and the G3 composite theory [25]. This new methodology has been referred to as G3CEP [21,22]. The mean absolute error for this method is 5.4 kJ mol<sup>-1</sup> compared to 4.9 kJ mol<sup>-1</sup> from the original all-electron version, taking into account a set of experimental data from the G3/05 test set [26].

Similarly, Rocha et al. [27] developed the G3(MP2)//B3-CEP theory by combining the CEP pseudopotential and the G3(MP2)//B3 theory [28]. The mean absolute errors for the G3(MP2)//B3-CEP calculations and the G3(MP2)//B3 all-electron calculations were 6.7 kJ mol<sup>-1</sup> and 5.9 kJ mol<sup>-1</sup>, respectively, when compared to the experimental data for a set of 446 available thermochemical and spectroscopic results in the gas phase. The CPU time using either G3CEP, or any version including pseudopotential, is significantly reduced [21,22,27,29–31].

The successful combination of pseudopotential and composite methods regarding accuracy and computational time reduction inspired the development of other alternatives such as G3(MP2)-CEP [29], G4CEP [30] and W1CEP [31] as well as applications for the elucidation of the mechanism of nitration of phenol [32] or the determination of internal rotational barriers of a set of compounds [33]. The simplicity of G3(MP2)-CEP and its all-electron version, G3(MP2), compared to most other composite methods provides conditions to apply them to larger systems where rigorous accurate ab initio methods would not be feasible.

Based on the excellent performance of the composite methods, the objective of this paper is to analyze the capabilities of one of the most recent developments, G3(MP2)-CEP, to analyze the main energetic factors governing a set of selected Diels-Alder reactions and to compare it with the performance of the respective all-electron version, G3(MP2). The selected Diels-Alder reactions in the gas phase considered the following reactants: (1) cyclopropene and cyclopentadiene, (2) cyclopentene and cyclopentadiene, (3) cyclopentadiene and acrylonitrile, (4) cyclohexadiene and acrylonitrile, (5) cycloheptadiene and acrylonitrile and (6) cyclopentadiene and maleic anhydride. These diene/dienophile pairs were selected because they have different experimental yields. In some cases, simply changing the size of the ring is enough to reverse the proportion of the products formed.

## 2. Computational methods

The G3(MP2)-CEP theory is characterized by the same sequence of calculations of the G3(MP2) all-electron theory by substituting the core electrons with pseudopotentials. The procedure for obtaining the final G3(MP2)-CEP energy can be summarized as follows [29]:

$$E_{G3(MP2)-CEP} = E[QCISD(T)/CEP - P31G(d)] + \Delta E_{CEP-G3MP2large} + E_{SO} + E_{ZPE} + \Delta E_{HLC} \quad (1)$$

where  $E[QCISD(T)/CEP - P31G(d)]$  is the reference energy and is improved by the following corrections:

- basis set size:  $\Delta E_{CEP-G3MP2large} = E[MP2/CEP - G3MP2large] - E[MP2/CEP - P31G(d)]$ ;
- spin-orbit effects:  $E_{SO}$ , obtained from experimental data or high-level calculations for a few atoms and molecules;
- zero-point energy and other thermal effects if the temperature is not 0 K,  $E_{ZPE}$ ;
- empirical *High-Level Correction* (HLC) for any additional effects not described by the previous corrections.

$\Delta E_{HLC}$  is defined by four general parameters,  $A$ ,  $B$ ,  $C$  and  $D$ , obtained from the minimization of the absolute error between calculated properties with respect to reliable experimental data and depends on the number of alpha ( $n_\alpha$ ) and beta ( $n_\beta$ ) valence electrons. Parameters  $A$  and  $B$  are associated with molecules, and  $C$  and  $D$  with atoms by the following expressions:

$E_{HLC} = -An_\beta - B(n_\alpha - n_\beta)$  and  $E_{HLC} = -Cn_\beta - D(n_\alpha - n_\beta)$ , respectively. In this work the parameters were obtained from reference [29].

All transition states (TS) were characterized by a single imaginary frequency and then submitted to the Intrinsic Reaction Coordinate (IRC) calculation at the MP2/CEP-P31G(d) level of theory. All calculations were performed with the Gaussian 09 program [34].

## 3. General discussion

The comparison of the energetic behavior of G3(MP2) and G3(MP2)-CEP was analyzed with respect to the six Diels-Alder reactions mentioned previously: (1) cyclopropene and cyclopentadiene, (2) cyclopentene and cyclopentadiene, (3) cyclopentadiene and acrylonitrile, (4) cyclohexadiene and acrylonitrile, (5) cycloheptadiene and acrylonitrile and (6) cyclopentadiene and maleic anhydride.

Table 1 shows the relative composite energies (at 0 K) and Gibbs energies (at 298 K) calculated by both levels of theory for all reactions, as well as some results from the literature.  $\Delta E_{TS}$  is the difference between the transition state energy (TS) and the reactant energy ( $\Delta E_{TS} = E_{TS} - E_{REACTANTS}$ ).  $\Delta E_R$  corresponds to the energy difference between products and reactants ( $\Delta E_R = E_{PRODUCTS} - E_{REACTANTS}$ ).  $\Delta G_{TS}$  and  $\Delta G_R$  are the analogous definitions with respect to the Gibbs energy. If the composite energies from Table 1 are compared, the results between the G3(MP2)-CEP and G3(MP2) usually differ by approximately 8.4 kJ mol<sup>-1</sup> for almost all the calculations. Reactions 4 and 6 present a larger difference, around 16.7 kJ mol<sup>-1</sup> for  $\Delta E_R$ . These differences are not significant if we consider relative energies,  $\delta\Delta E_{TS} = \Delta E_{TS(EXO)} - \Delta E_{TS(ENDO)}$  or  $\delta\Delta E_R = \Delta E_{R(EXO)} - \Delta E_{R(ENDO)}$ . The variations between methods do not exceed 1.3 kJ mol<sup>-1</sup> for reactions 2, 3, 4 and 5. Reactions 1 and 6 present a larger energy variation, but do not exceed 4.2 kJ mol<sup>-1</sup>. Almost the same results are observed when  $\delta\Delta G_{TS}$  and  $\delta\Delta G_R$  are compared. Therefore, the quantitative behavior as well as their qualitative tendency is consistent and considerably more accurate than using either G3(MP2) or G3(MP2)-CEP.

The tendencies associated with the experimental yield based on the relative energies will be studied in a systematic way, analyzing the characteristics of the group of reactions separately.

### 3.1. Reactions 1 and 2

It is known that the experimental ratio between the endo/exo adducts is strongly altered when cyclopropene is replaced by cyclopentene in a reaction with cyclopentadiene. This pair of reactions is represented in Figs. 1 and 2.

Table 1 shows for reaction 1 that the barrier for TS<sub>endo</sub> is lower than TS<sub>exo</sub> by 17.6 and 18.8 kJ mol<sup>-1</sup> for G3(MP2) and G3(MP2)-CEP, respectively. However, the exo analog is still the most

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