The Source of the *endo* Rule in the Diels−Alder Reaction: Are Secondary Orbital Interactions Really Necessary?

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The *endo* preference in Diels–Alder reactions is usually attributed to the occurrence of attractive Secondary Orbital Interactions (SOI), whereas other interaction mechanisms (primary interactions, closed-shell repulsions, electrostatics) are assumed to be identical for both *endo* and *exo* approaches. However, analysis of the parallel approximation between *s-trans* butadiene and fumaronitrile shows that SOI is overcome by closed-shell repulsions. Furthermore, the study of several reactions (cyclopentadiene + maleic anhydride, cyclobutadiene + cyclobutenedione, cyclobutadiene + norbornadiene) indicates the absence of a net attraction for the atom pairs involved in SOI. As a conclusion, the *endo* preference is not due to the occurrence of an attractive interaction between the atom pairs involved in SOI and so this concept is unnecessary.

Introduction

It is well known that most Diels−Alder reactions between simple reactants lead preferentially to the *endo* adduct.[1] However, the reason for such behavior has become the subject of great debate in recent years. The most commonly used explanation is based on the existence of a stabilizing overlap (called a Secondary Orbital Interaction, SOI) between the frontier molecular orbitals of the reactants at centers that do not participate in the formation of σ bonds in the *endo* approach.[2] However, this hypothesis has been called into question by our research, which has shown that the main arguments suggesting the existence of SOI are inconclusive.[3]

A method to quantify the SOI has been proposed by Cossío and co-workers.[4] The application of this methodology to the cyclopentadiene + maleic anhydride cycloaddition shows significant stabilization of the *endo* transition state (TS) attributed to SOI. The authors concluded from these results that "*SOI do exist and are responsible for at least an important part of the observed stereocontrol*".[4]

However, analysis of the methodology used in the study outlined above raises questions about the validity of several quite wide-ranging approximations applied to the Klopman−Salem equation. Firstly, the magnitudes of the primary interactions (i.e., those leading to the formation of new σ bonds) are assumed to be equal in both *endo* and *exo* approaches. More interestingly, the role of electrostatic and closed-shell interactions are neglected in spite of the known influence of these interactions on the *endo*/*exo* selectivity of some Diels−Alder reactions (e.g. furan + cyclopropenone[5] or cyclopentadiene + cyclopentene[6]). Finally, a numerical bias derived from the assumption of a strictly parallel approach between the two reactants and the use of the AM1 method (a method that wrongly predicts an increase in the activation barrier of Diels−Alder reactions when the number of electron-withdrawing groups in the dienophile is increased)[7,8] may also be possible.

Given these circumstances, the conclusions drawn by Cossío must be open to question. For example, the energy analysis is focused on the interaction that exists between occupied and vacant frontier molecular orbitals (MOs) for the approximation between the secondary centers. It is therefore not surprising to find a certain stabilization energy in the approach between the reactants, since the Perturbation Molecular Orbital (PMO) theory predicts a negative interaction energy for any occupied−vacant MO pair (unless a long distance is involved or particular symmetry requirements are met). From this perspective, the statement "*SOI do exist*" is self-evident and numerical studies are unnecessary to prove it.

However, the restriction of the analysis to the occupied−vacant MO interactions would lead to the paradoxical conclusion that the approximation between any pair of molecular fragments leads to a stabilization in all cases (including, for example, two colliding *tert*-butyl groups). In contrast, it is our opinion that such a discussion should include *all* the possible mechanism interactions between the atom pairs involved. In this paper we wish to revisit the role of SOI in the Diels−Alder reaction by considering the net

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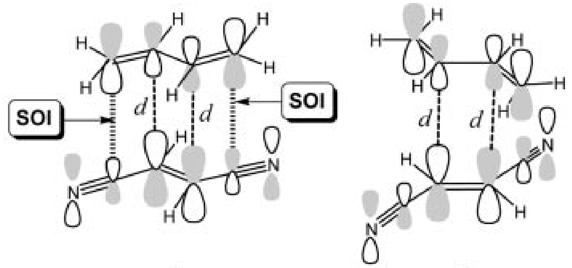
energy effect of the approximation between the corresponding atoms in a number of real and ideal systems that have different features. In this way, the attribution of the *endo* rule to the SOI hypothesis would only be satisfactory if a net attractive interaction between the involved atom pairs is found.

Results and Discussion

A Computational Laboratory for SOI: The *s-trans*-Butadiene + Fumaronitrile System

The system in question (Scheme 1) represents an idealized situation that is optimal to estimate the extent of SOI. Both reactants are common in Diels–Alder reactions and reflect the general behavior expected. The parallel approximation between the two molecules placed at a variable distance (*d*) allows the maximization of the magnitude of the SOI, with the influence of first-order orbital interactions being negligible due to geometric requirements. Substituents on the main chain in both molecules are small in size and are oriented in different directions, thus avoiding peripheral steric repulsions. Finally, the C_2 symmetry of the system allows the interpretation to be simplified.



1 **2**

Scheme 1. *s-trans*-Butadiene + fumaronitrile complexes that have (**1**) or lack (**2**) SOI

Figure 1 shows the interaction energy (defined as the energy difference between a complex and the corresponding reactants) for both **1** and **2** as a function of the distance, *d*, according to MP2/6-311+G(2*df*)//MP2/6-31G* calculations. The results show hook-shaped plots for the two systems, with the minima situated at 3.3 Å (**1**) and 3.2 Å (**2**).

It should be noted that the structure lacking SOI is the most stable geometry at any distance considered, with the interaction energies showing a trend to convergence at distances longer than 2.6 Å. A significant role of the Basis Set Superposition Error (BSSE) for the relative energies can be disregarded since the counterpoise corrections for **1** and **2** at *d* = 3.0 Å are 2.197 kcal·mol^{-1} and 2.169 kcal·mol^{-1}, respectively. These results seem to indicate that the approximation of the atoms involved in SOI actually gives rise to a repulsive effect.

For the minimum energy of structure **1**, the carbon atoms involved in the SOIs are 3.314 Å apart, a value that is slightly higher than the typical distances between atoms involved in SOI (e.g., 3.096 Å for the *s-cis*-butadiene + fumaronitrile TS calculated at the same level, vide infra). For this reason, the corresponding geometry obtained at *d* = 3.0 Å (SOI atoms separated by 3.133 Å) was the only one used for comparison of **1** with other chemical structures.

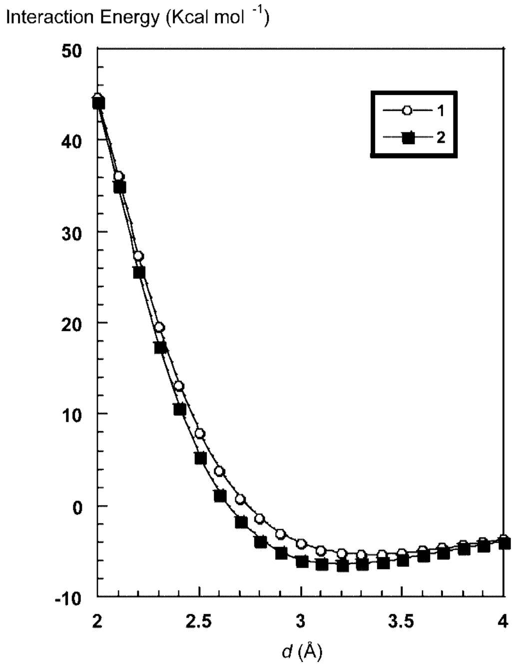


Figure 1. MP2/6-311+G(2*df*)//MP2/6-31G* interaction energies for complexes **1** (circles) and **2** (squares)

It is known that the overlap between localized π- and π*-orbitals can lead to significant stabilization of the *endo* TS relative to the *exo* state (1.48 kcal·mol^{-1} for each interaction in the cyclopentadiene + maleic anhydride reaction).[4] In our system, an NBO analysis[9] of the transition state for the *s-cis*-butadiene + fumaronitrile Diels–Alder reaction (Figure 2) indicates a significant interaction between the localized π- and π*-orbitals between the *endo* nitrile group and the closest diene double bond (1.14 kcal·mol^{-1} for the diene→dienophile delocalization and 0.13 kcal·mol^{-1} in the reverse case).

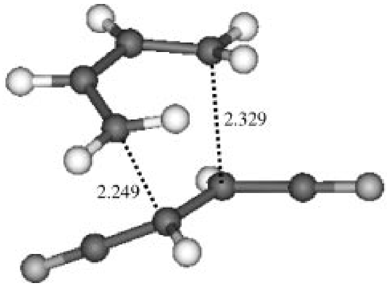


Figure 2. Transition state of the reaction between *s-cis*-butadiene and fumaronitrile (**3**), according to MP2/6-31G* calculations

In the case of structure **1** (*d* = 3.0 Å), a similar analysis shows an even greater degree of stabilization (0.94 kcal·mol^{-1} and 0.75 kcal·mol^{-1}, depending on the delocalization direction) for each butadiene double bond/fumaronitrile cyano interaction. In spite of this apparently contradictory result, it should be noted that the net preference (at $d = 3.0$ Å) for structure **2** is completely compatible with the existence of significant stabilization (3.38 kcal·mol^{-1}) of **1** due to SOI by 1.80 kcal·mol^{-1}. The apparent discrepancy can be attributed to the role of closed-shell repulsions. Thus, NBO calculations for structures **1** and **2** (both at $d = 3.0$ Å) indicate a larger total pairwise steric exchange energy between butadiene and fumaronitrile in the former case (by 4.63 kcal·mol^{-1}). The differential destabilization of **1** can be essentially attributed to the interaction of each butadiene C−C double bond with nearby fumaronitrile bonds: nitrile (by 2.66 kcal·mol^{-1}), C−C single bond (by 0.93 kcal·mol^{-1}) or C−H bond (stabilized by 1.41 kcal·mol^{-1}).

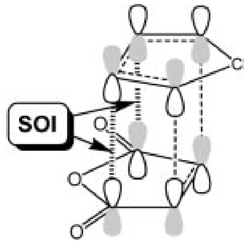
A major role for the closed-shell repulsions between atoms involved in SOI can also be observed in the TS of the *s-cis*-butadiene + fumaronitrile reaction (Figure 2). The pairwise steric exchange energy between butadiene and each fumaronitrile C−C−N grouping clearly depends on the orientation of the latter (*endo*: 20.18 kcal·mol^{-1}; *exo*: 13.03 kcal·mol^{-1}). In contrast, the corresponding repulsions between butadiene and each fumaronitrile C−H bond were found to be very similar (*endo*: 10.54 kcal·mol^{-1}; *exo*: 11.37 kcal·mol^{-1}).

It therefore appears that closed-shell repulsions can prevail over SOI attractions in the interactions between typical Diels−Alder reactants. This *exo*-leading trend must then be combined with other *endo*-favoring interactions in order to justify the *endo* rule observed in most Diels−Alder reactions.

Diels−Alder Reactions

Cyclopentadiene + Maleic Anhydride

This cycloaddition is considered as a typical example to explain the nature of SOI (Scheme 2),[10] and was chosen by Cossío and co-workers to evaluate the energies involved in these interactions using B3LYP/6-31G* calculations.[4]



Scheme 2. The *endo* approach for the cyclopentadiene + maleic anhydride reaction

The corresponding *endo* TS is shown in Figure 3; the geometrical features match those reported in the aforementioned work.[4] Those results show a significant interaction (−1.48 kcal·mol^{-1}) between each C=O π* molecular orbital of maleic anhydride and the closest localized C=C π-orbital of cyclopentadiene.[4] Our NBO results confirm this value, but the calculation of the pairwise steric exchange energy for each C=C π/C=O π interaction gave a value of +3.47 kcal·mol^{-1}. These results indicate that the attractive effect of SOI is overcome by the closed-shell exchange repulsion, with the net interaction energy between the atom pairs involved in SOI thus being repulsive. This situation is in agreement with the results obtained in our "computational laboratory of SOI" — the lack of a global attractive effect allows one to explain the relatively long distance that exists between the atoms involved in SOI (2.962 Å).

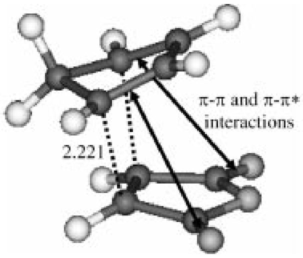
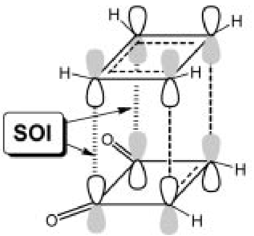


Figure 3. The *endo* transition state of the cyclopentadiene + maleic anhydride reaction, indicating π-π and π-π* interactions (at the B3LYP/6-31G* level)

The conclusion drawn above can be supported by experimental data. For example, the *endo* preference observed in the reactions of cyclopentadiene with cyclopentene and *cis*-3,4-dichlorocyclobutene[6] reflects the presence of significant steric repulsions between the methylene group of cyclopentadiene and the dienophile in the *exo* approach. In agreement with this result, the experimental *endo* preference of the cyclopentadiene + maleic anhydride reaction (2.5 kcal·mol^{-1})[11] is significantly reduced when the diene is replaced by butadiene (1.2 kcal·mol^{-1})[11] or furan (0.2 kcal·mol^{-1}).[12] Furthermore, a theoretical study 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.[13] As a logical conclusion, the *endo* preference of the cyclopentadiene + 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)[12] may also play a role.

Cyclobutadiene + Cyclobutenedione

Several factors can be expected to favor the appearance of SOI in a reaction. These include the proximity that can be envisaged between the secondary centers involved because of the molecular geometries of the reactants, the occurrence of high atomic coefficients in the corresponding frontier MOs, and the lack of significant destabilizing interactions (such as steric repulsions) between atoms other than those involved in the SOI. All of these "beneficial" properties are present in the *endo* TS of the cyclobutadiene + cyclobutenedione cycloaddition (Scheme 3).



Scheme 3. The *endo* approach for the cyclobutadiene + cyclobutenedione reaction

In order to obtain an accurate estimate of the *endo* preference for this reaction, MP2/6-31G* optimizations were carried out for both *endo* and *exo* TSs (shown in Figure 4) as well as MP2/6-311+G(2*d*) single-point energy calculations for the corresponding geometries. The results indicate very similar energies for both TSs, with the *endo* structure being slightly favored (by 0.1 kcal·mol^{-1} at the double-zeta level; 0.2 kcal·mol^{-1} at the triple-zeta level).

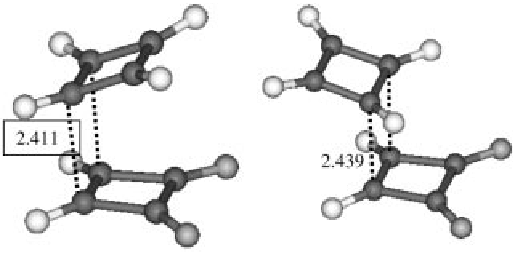


Figure 4. Structures of both *endo* (left) and *exo* (right) transition states for the cyclobutadiene + cyclobutenedione reaction, according to MP2/6-31G* calculations

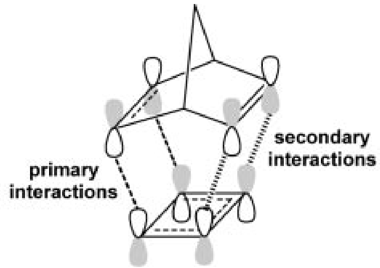
The geometries of the transition states provide interesting information. The angles formed by the incipient σ bonds and the secondary centers at the *exo* TS (105.4° for cyclobutadiene, 90.8° for cyclobutenedione) are significantly larger in the *endo* TS (108.7° and 95.0°, respectively). In contrast, the angles formed by the incipient σ bonds and the vicinal carbon−hydrogen bonds are lower for the *exo* TS (93.4° for cyclobutadiene, 93.2° for cyclobutenedione) than the *endo* structure (93.9° and 96.9°, respectively). Taking into account that significant differences in the pyramidalization of the carbon atoms are not found, it can be concluded that these results indicate the existence of a net repulsion between the secondary centers.

The NBO analysis of the *endo* TS (at MP2/6-31G* level) confirms the net repulsion that exists between secondary centers. The π-π* interactions between each carbonyl group from cyclobutenedione and the closest double bond from the cyclobutadiene are 3.17 kcal·mol^{-1} for the diene→dienophile interaction but only 0.48 kcal·mol^{-1} for the reverse interaction. On the other hand, the corresponding π-π repulsion between these groups is somewhat larger (4.07 kcal·mol^{-1}). Evidently, other interaction mechanisms can also be involved in the relative stability between *endo* and *exo* transition states. Thus, the *endo* preference (by 1.0 kcal·mol^{-1}) calculated at the B3LYP/6-31G* level allows us to suggest a significant role for dispersion forces, which are insufficiently described by density-functional methods.

The absence of a net stabilizing effect involved in SOI for a system specifically chosen to favor their occurrence could indicate that such interactions are even more disfavored in the general case. Indeed, theoretical studies on a large number of Diels−Alder reactions have shown that the atom pairs involved in SOIs are situated at relatively long distances from one another.[4,12,14−22]

Cyclobutadiene + Norbornadiene

SOI occurs due to the interaction between the reactive frontier molecular orbitals of both addends at secondary centers. Therefore, the interaction between the secondary centers of a reactant and a π-orbital from the other compound not participating in the bond rearrangement does not match with the classical definition of SOI. The energy involved in these non-SOI interactions can be estimated for the addition of cyclobutadiene to the *syn* face of norbornadiene by comparing the *endo* TS (Scheme 4) with the corresponding *exo* structure, according to MP2/6-31G* optimizations as well as MP2/6-311+G(2*d*) single-point energy calculations.



Scheme 4. The *endo syn* approach for the cyclobutadiene + norbornadiene reaction

Both *endo* and *exo* transition states corresponding to the approach of cyclobutadiene to norbornadiene are shown in Figure 5. These theoretical results indicate a concerted mechanism with early transition states. Thus, the lengths of the incipient bonds are 2.418 Å for the *endo* TS and 2.415 Å for the corresponding *exo* TS. The relative energies indicate a preference for the *endo* approach (by 1.8 kcal·mol^{-1} at the double-zeta level; 2.5 kcal·mol^{-1} at the triple-zeta

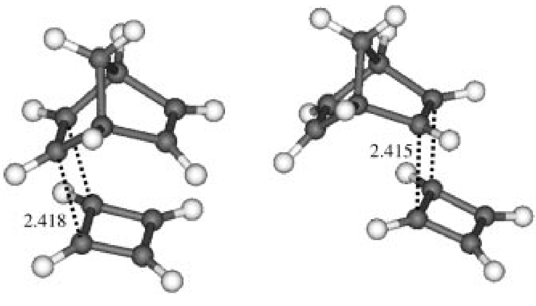


Figure 5. Structures of both *endo* (left) and *exo* (right) transition states for the approach of cyclobutadiene to the *syn* face of norbornadiene, according to MP2/6-31G* calculations

level). The lower *endo* preference calculated by means of theoretical methods that underestimate the dispersion forces (Hartree−Fock, triple-zeta basis: 1.2 kcal·mol^{-1}; DFT, double-zeta basis: 0.5 kcal·mol^{-1}) allows us to assume a significant role for these interactions in the *endo*/*exo* selectivity.

The NBO analysis of the *endo* TS allows an estimation of the magnitude of the secondary interactions between the nonreactive double bond of norbornadiene and the π-system of cyclobutadiene. It was found that the attractive interactions between occupied and vacant π molecular orbitals (1.67 kcal·mol^{-1} for each norbornadiene→cyclobutadiene interaction; 2.73 kcal·mol^{-1} for the reverse case) are overcome by the corresponding π-π closed-shell repulsions (5.51 kcal·mol^{-1} for each one). This means that a net repulsive effect is also found for the approximation between secondary centers of cyclobutadiene and the nonreactive π-system of norbornadiene.

The magnitude of these secondary interactions was also evaluated using the methodology proposed by Cossío and co-workers. The corresponding magnitude was quantified at five points (denoted **a**−**e**) on the intrinsic reaction coordinate (IRC; at the B3LYP/6-31G* level) for the *endo* approach by means of a mathematical formula that employs the atomic coefficients and energies of the frontier molecular orbitals calculated for the reactants with the AM1 method. In this case, both HOMO$_{\text{diene}}$−LUMO$_{\text{dienophile}}$ and LUMO$_{\text{diene}}$−HOMO$_{\text{dienophile}}$ delocalizations were considered for the evaluation of primary and secondary interactions. The results of this study are gathered in Table 1.

Table 1. Energy contributions for the primary and secondary interactions between frontier molecular orbitals along the IRC of the reaction between cyclobutadiene and norbornadiene

Point	R_{prim} [Å]	R_{sec} [Å]	ΔE_{prim} [kcal·mol^{-1}]	$\Delta E_{\text{prim+sec}}$ [kcal·mol^{-1}]
a	2.899	3.083	−0.46	−1.35
b	2.806	3.064	−0.65	−1.70
c	2.683	3.052	−1.14	−2.49
d	2.559	3.046	−1.51	−3.04
e	2.453	3.045	−2.12	−3.89

It can be seen that the approximation between the two reactants involves an increasing stabilization of both TSs through primary interactions (*exo* geometry) or the combination of primary and secondary interactions (*endo* structure). Furthermore, the reaction progress involves a decrease in the $\Delta E_{endo}/\Delta E_{exo}$ ratio despite an increase in the corresponding energy difference, a situation analogous to that reported for the cyclopentadiene + maleic anhydride reaction. More interestingly, the relative stabilization energy (1.77 kcal·mol^{-1}) at point **e** (distance between primary centers = 2.453 Å) is significantly larger than that reported for a similar point in the cyclopentadiene + maleic anhydride reaction (0.73 kcal·mol^{-1} for 2.463 Å).[4] However, as stated above, closed-shell repulsions between these centers are always superior, and the calculated *endo* preference is ascribed to dispersion forces.

It must therefore be concluded that a significant stabilization can be found for an interaction between occupied and vacant molecular orbitals irrespective of the direct participation of these orbitals in the electronic rearrangement involved in the reaction. Thus, energy stabilizations calculated in theoretical studies for SOI are not specifically indicative of these interactions; rather, they are a general feature of any pair of molecular fragments and do not seem to be the origin of *endo* selectivity in any example considered here.

Conclusions

A "laboratory of SOI" has been designed by considering the parallel approximation between *s-trans*-butadiene and fumaronitrile. The results indicate that SOI is overcome by closed-shell repulsions. The same conclusion is reached for the TS of the *s-cis*-butadiene + fumaronitrile Diels−Alder reaction. Analogously, an NBO analysis of the *endo* TS for the cyclopentadiene + maleic anhydride reaction shows that the attractive effect of the C=C π/C=O π* SOI is overcome by the closed-shell repulsion between the corresponding C=C π/C=O π orbitals. The *endo* preference observed for this reaction must therefore be attributed to other factors, including the steric repulsions induced by the methylene group in the *exo* TS.

An *exo* preference has been found for the cyclobutadiene + cyclobutenedione reaction in spite of the geometric and energetic features favoring the appearance of SOI in the *endo* TS. Therefore, evidence for the occurrence of these interactions is not found even in a system specifically chosen to be favorable on an ad hoc basis.

The magnitude of the non-SOI interactions between the secondary centers of cyclobutadiene and a norbornadiene C=C bond not involved in the π rearrangement has been analyzed using a method described to estimate the magnitude of SOI. The results indicate that these non-SOI interactions are larger than SOI in the cyclopentadiene + maleic anhydride reaction, thereby showing that the calculated interaction between occupied and vacant molecular orbitals is not specially favored by the corresponding atoms belonging to the reactive system.

In summary, the concept of SOI was based on the assumption that closed-shell repulsions were identical in *endo* and *exo* approaches. However, the opposite situation is found and classical SOI is overcome by closed-shell repulsions in all cases considered here, even in systems specially designed to favor the former interactions. Therefore, the concept of SOI is unnecessary and should be abandoned by chemists as a general explanation for the *endo* preference in Diels−Alder reactions.

Experimental Section

General Remarks: The MP2 correlation level was used by default throughout this work because of its satisfactory performance for intermolecular interactions in related systems. For example, interaction energies calculated at the MP2 level for ethylene and benzene dimers, as well as the benzene−ethylene complex, are close to CCSD(T) values.[23] The B3LYP functional[24−26] was used for the IRC calculations on the cyclobutadiene + norbornadiene reaction for the sake of comparison with the methodology used by Cossío. Both MP2 and B3LYP methods were used with the 6-31G* basis set for the geometry optimization of transition states. In addition, single-point calculations were carried out for MP2/6-31G* geometries for the *s-trans*-butadiene + fumaronitrile system [at the MP2/6-311+G(2*df*) level] as well as the TSs of the cyclobutadiene reactions [at the MP2/6-311+G(2*d*) level]. The transition states were characterized by the presence of a unique negative eigenvalue of the analytical Hessian. Geometry optimization of TSs was carried out using the Gaussian 98 program package.[27] Energy corrections (ZPE, vibrational, solvation, BSSE) were not considered in this work. Natural Bond Orbital calculations (by using spherical coordinates used for angular functions of *d* and *f* orbitals) were carried out with the NBO 5.0 program[9] as implemented in the NWChem package.[28]

Supporting Information: Total and relative energies of structures **1** and **2** at different distances as well as total energies and Cartesian coordinates of the transition states (see also footnote on the first page of this article).

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