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Direct Evaluation of Secondary Orbital Interactions in the Diels−Alder Reaction between Cyclopentadiene and Maleic Anhydride

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Secondary orbital interactions (SOI) were proposed by Hoffmann and Woodward[1] to rationalize the empirical endo rule formulated by Alder and Stein.[2] According to this rule, the major stereoisomer in Diels−Alder reactions is that it is formed through a maximum accumulation of double bonds. In [4 + 2] thermal cycloadditions, SOI consist of a stabilizing two-electron interaction between atomic orbitals not involved in the formation or cleavage of σ bonds.

Since the formulation of SOI, it has become a textbook model to explain stereoselectivity in pericyclic reactions.[3] However, the validity of the model or even the existence of SOI has been questioned.[4] Given the importance of this problem and its controversial situation, we have investigated a classical [4 + 2] thermal cycloaddition whose experimentally observed endo stereoselectivity has been attributed to SOI, namely the Diels−Alder reaction between cyclopentadiene and maleic anhydride (Scheme 1).

Because of the C_{2v} symmetry of both reactants, the selected reaction does not raise regiochemical and conformational issues and the analysis of the corresponding reaction coordinates is simpler. We have calculated the formation of both *exo*- and *endo*-**3** cycloadducts at the B3LYP/6-31G* level[5,6] (Scheme 1). The chief geometric and energetic features of corresponding transition structures *endo*- and *exo*-**TS** at the same computational level are depicted in Figure 1. According to our results, both transition structures are quite similar in the gas phase and in benzene solution ($\epsilon = 2.27$) simulated by means of the Onsager (L1A1) and SCIPCM models.[7] Our calculations also indicate that *endo*-**TS** is 1.01 kcal/mol more stable than *exo*-**TS** in the gas phase, and 1.12 kcal/mol in benzene solution (B3LYP/6-31G*+ΔZPVE and B3LYP/(SCIPCM)//B3LYP−(L1A1)/6-31G*+ΔZPVE results, respectively). Thus, in this reaction the stereochemical outcome is not determined by solvent effects, as found in other Diels−Alder reactions.[8] This energetic difference corresponds to a 91:9 *endo:exo* kinetic ratio, in good agreement with experimental results.[9]

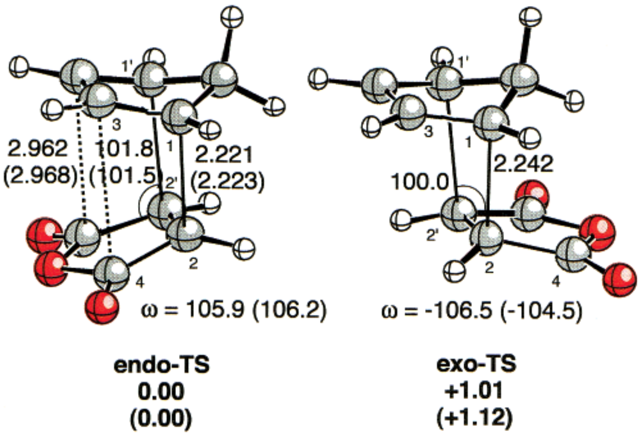
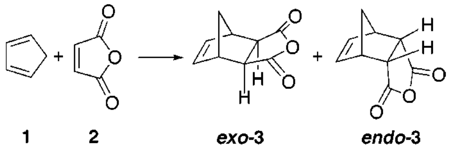


Figure 1. Fully optimized B3LYP/6-31G* transition structures associated with formation of cycloadducts *endo*- and *exo*-**3**. Bond distances are given in Å and deg, respectively. ω is the C4−C2−C2′−C1′ dihedral angle. Numbers in brackets correspond to results obtained in simulated benzene solution. Bold numbers are the relative energies between both transition structures, given in kcal/mol.

Scheme 1



To evaluate the effect of SOI on the stereochemical outcome of the reaction, we have studied the two-electron interaction between the HOMO of **1** and the LUMO of **2** applying second-order perturbation theory[10] (Figure 2).

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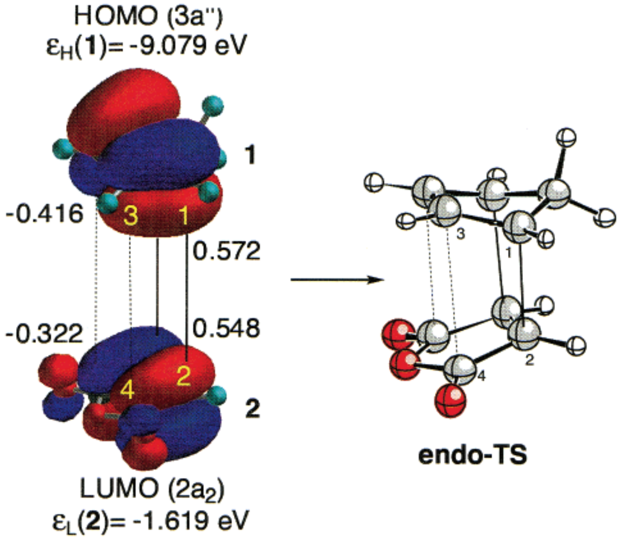


Figure 2. FMOs of reactants **1** and **2** computed at the AM1 level. Numbers next to the atoms are the respective expansion coefficients. Orbital energies (ϵ), expansion coefficients, and atom numbering is that used in eqs 1−7. All these magnitudes have been computed at the AM1 level. The ball-and-stick representation of *endo*-**TS** has been included in order to facilitate the identification of the different reactive centers.

According to this model, if primary and secondary interactions are involved, the stabilization energy ΔE_{p+s} associated with the initial stages of the cycloaddition can be described as

$$\Delta E_{\mathrm{p+s}} = \frac{8}{\Delta\epsilon}(p^2 + 2\mathrm{ps} + s^2) \qquad (1)$$

where $\Delta\epsilon = \epsilon_{\mathrm{H}}(\mathbf{1}) - \epsilon_{\mathrm{L}}(\mathbf{2})$ and p is the primary interaction term (namely, that leads to formation of the σ bonds) which is given by

$$p = c_1^{\ \mathrm{H}} c_2^{\ \mathrm{L}} \beta_{12} \qquad (2)$$

Similarly, the secondary interaction term is

$$s = c_3^{\ \mathrm{H}} c_4^{\ \mathrm{L}} \beta_{34} \qquad (3)$$

In both eqs 2 and 3, β_{ij} denotes the resonance integral between the i and j atoms (Figure 2) and c_i^{H}, c_j^{H} are the atomic expansion coefficients of the HOMO and LUMO of **1** and **2**, respectively. If only the primary interactions were relevant, the stabilization energy ΔE_{p} could be reduced to

$$\Delta E_{\mathrm{p}} = \frac{8}{\Delta\epsilon} p^2 \qquad (4)$$

In consequence, if other interactions are supposed to be similar for endo and exo approaches, the activation energy ratio associated with formation of *endo*- and *exo*-**3**

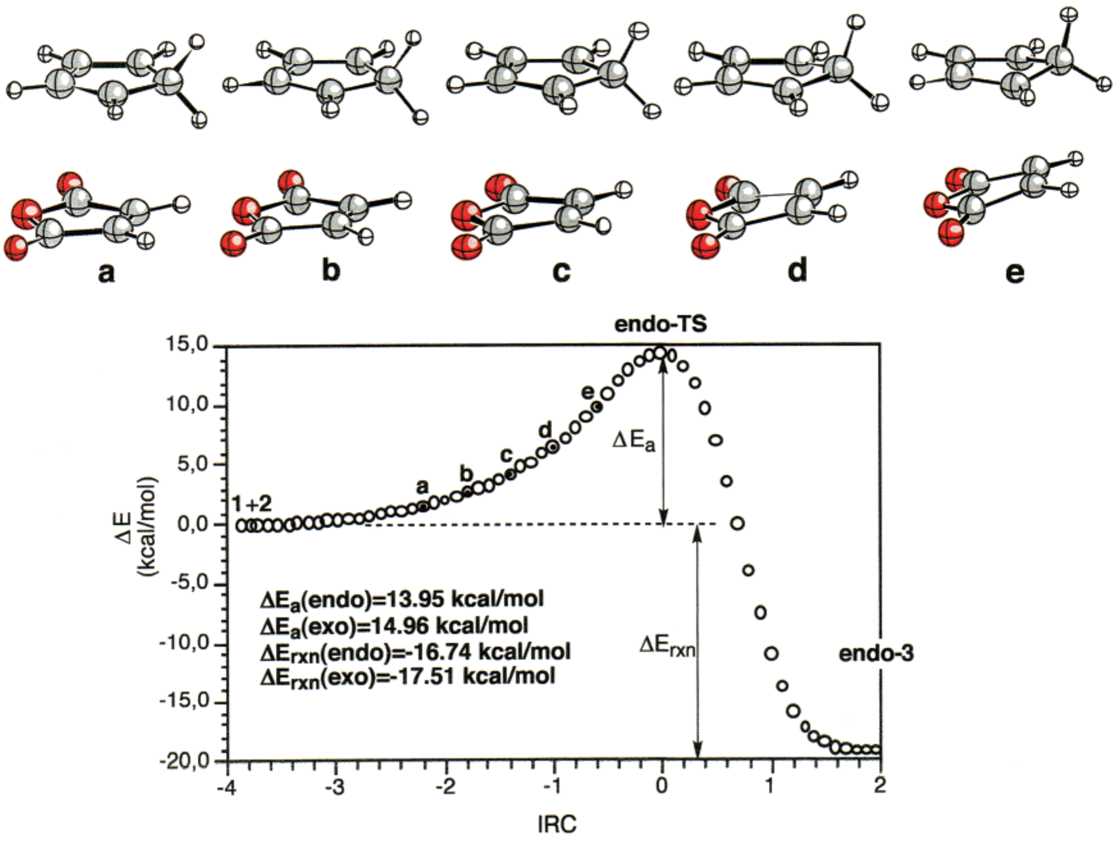


Figure 3. Intrinsic reaction coordinate (IRC) for the **1**+**2** → *endo*-**3** transformation, computed at the B3LYP/6-31G* level. Points **a**−**e** are those selected to compute the data reported in Figure 1. Activation energies (ΔE_{a}) and reaction energies (ΔE_{rxn}) include zero-point vibrational energy corrections (not scaled).

Table 1. Evolution of the Magnitudes Associated with the Secondary Orbital Interactions along the IRC of the Reaction between Cyclopentadiene and Maleic Anhydride

	R_{12}	R_{34}	S_{12}	S_{34}	s	p	$\Delta E_{\mathrm{p+s}}$	ΔE_{p}	ΔE_{endo}:ΔE_{exo}	$\lvert\Delta E_{\mathrm{endo}} - \Delta E_{\mathrm{exo}}\rvert$
a	3.196	3.246	0.031	0.028	−0.68	−1.74	−0.27	−0.14	1.93	0.13
b	3.117	3.203	0.036	0.031	−0.74	−2.03	−0.36	−0.19	1.89	0.17
c	2.957	3.131	0.050	0.036	−0.85	−2.78	−0.61	−0.36	1.69	0.25
d	2.746	3.057	0.072	0.041	−0.98	−4.03	−1.16	−0.75	1.55	0.41
e	2.463	2.986	0.116	0.047	−1.12	−6.46	−2.67	−1.94	1.38	0.73

[a] For the position of points **a**−**e** along the IRC, see Figure 3. For the meaning of the magnitudes see eqs 1−7. [b] All distances $R_{1,2}$ and $R_{3,4}$ are given in Å. [c] Magnitudes *s*, *p*, $\Delta E_{\mathrm{s+p}}$, ΔE_{p}, and $\lvert\Delta E_{\mathrm{endo}}$-$\Delta E_{\mathrm{exo}}\rvert$ are given in kcal/mol.

can be approximated as

$$\frac{\Delta E_{\mathrm{endo}}}{\Delta E_{\mathrm{exo}}} \approx \frac{\Delta E_{\mathrm{p+s}}}{\Delta E_{\mathrm{p}}} = 1 + \frac{s}{p}\left(2 + \frac{s}{p}\right) \qquad (5)$$

Since $\Delta\epsilon$ and c_i^{H}, c_j^{H} are readily accessible data from standard SCF-MO calculations, only the resonance integrals β_{ij} remain to be evaluated in order to solve eqs 1−5. This can be easily achieved by means of the Mulliken[11] approximation:

$$\beta_{ij} = \frac{1}{2}\,(\beta_i^\circ + \beta_j^\circ)S_{ij} \qquad (6)$$

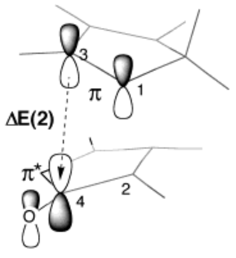
Where β_i° and β_j° are fixed parameters for atoms *i* and *j*, and S_{ij} is the corresponding overlap integral. Since the SOI considered take place between carbon atoms, in this particular case $\beta_i^\circ = \beta_j^\circ = \beta_{2p}^c$. In addition, S_{ij} can be evaluated according to the Mulliken formulas for 2p−2p σ-overlap.[12] Therefore, eq 6 transforms into

$$\beta_{ij} = \beta_{2p}^c\left[-1 - \zeta R_{ij} - \frac{\zeta^2 R_{ij}^{\,2}}{5} + 2\,\frac{\zeta^3 R_{ij}^{\,3}}{15} + \frac{\zeta^4 R_{ij}^{\,4}}{15}\right]\exp(-\zeta R_{ij}) \qquad (7)$$

Where ζ is the Slater exponent and R_{ij} is the internuclear distance. We have used the values $\beta_{2p}^c = -178.01$ kcal/mol and $\zeta = 3.185$ Å^{-1}, according to the optimized values proposed by Dewar.[13]

We have solved eqs 1−7 at different points of the intrinsic reaction coordinate (IRC) calculated for the **1**+**2** → *endo*-**3b** transformation. We have selected several representative points for which $S_{ij} \leq 0.1$ (Figure 3), and the results obtained are given in Table 1. According to these data, the R_{12} distances shrink more quickly along the IRC than the R_{34} distances, the latter remaining close to 3 Å (See also Figure 3). However, the secondary interaction terms *s*, although smaller than the corresponding *p* terms, are appreciable. In addition, although the ΔE_{endo}:ΔE_{exo} ratio is larger at the early stages of the reaction, the $\lvert\Delta E_{\mathrm{endo}} - \Delta E_{\mathrm{exo}}\rvert$ values follow the reverse trend because of the cross term *2ps* of eq 1. Thus, at the point **e** this difference is ca. 0.7 kcal/mol (see Table 1). It is likely that this difference is larger in the corresponding transition state. In effect, the Natural Bonding Analysis[14] on *endo*-**TS** at the B3LYP/6-31G* level shows a two-electron interaction between the localized $C_1{=}C_3$ π and $C_4{=}O$ π^* orbitals, whose associated second-order energy is ca. 1.5 kcal/mol (see Scheme 2).

Scheme 2. Two-Electron Interaction between π(C1═C3) and π*(C4═O) Localized Orbitals in *endo*-TS[a]



$$\Delta E(2) = -2\,\frac{\langle \pi^* | F | \pi \rangle^2}{\varepsilon(\pi^*) - \varepsilon(\pi)} = -1.48\,kcal/mol$$

[a] $\Delta E(2)$ is the second-order perturbation energy associated with the interaction, *F* is the Fock operator, π and π^* are the natural orbitals, $\epsilon(\pi)$ and $\epsilon(\pi^*)$ being the corresponding orbital energies.

In summary, we have evaluated directly the magnitude of SOI for a classical endo-oriented Diels−Alder reaction, and we have found that SOI do exist and are responsible for at least an important part of the observed stereocontrol. Although the absolute magnitude of this kind of interactions is small, its impact on the stereochemical outcome is very important, because of the exponential relationship between the difference in activation energies and the kinetic product ratio. Of course, other factors can operate in different cycloadditions, and their relative importance can vary from one case to another, but the magnitude of SOI cannot be discarded a priori.

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Supporting Information Available: Cartesian coordinates, electronic energies, and zero-point vibrational energies (ZPVEs) of stationary points **1**, **2**, *endo*-**TS**, *exo*-**TS**, *endo*-**3**, and *exo*-**3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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