

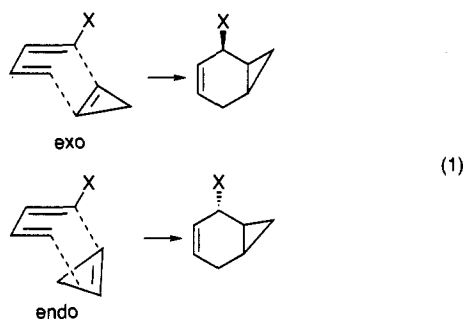
# Evidence for the Dominant Role of Secondary Orbital Interactions in Determining the Stereochemistry of the Diels–Alder Reaction: The Case of Cyclopropene†

Yitzhak Apeloig\* and Eynatte Matzner

Department of Chemistry  
Technion—Israel Institute of Technology, Haifa 32000, Israel

Received January 18, 1995

The Diels–Alder (DA) reaction is one of the most important reactions both in synthesis and in its mechanistic implications.<sup>1a</sup> Much attention was devoted to the facial stereoselectivity, i.e., *exo* vs *endo* approach of the diene to the dienophile,<sup>1a</sup> for which cyclopropene (CP) is the simplest example (eq 1).



Alder rationalized the predominant *endo* selectivity in many DA reactions (the “*endo rule*”) as due to “maximum accumulation of unsaturation”.<sup>1b</sup> Woodward and Hoffmann<sup>2</sup> postulated that *endo* stereoselectivity results from favorable “secondary orbital interactions” (SOI) between atoms in the diene and dienophile that do not become bonded in the adduct. Such interactions are significant only in the *endo* transition state. The SOI concept originally proposed<sup>2</sup> for  $\pi$ -type substituents (e.g., CN, CHO) was later extended to alkyl-substituted dienophiles because they possess  $\pi_{CH_2}$ -type orbitals;<sup>3</sup> e.g., cyclopropene.<sup>4</sup>

The attractive concept of SOI is now deeply embedded in organic chemistry.<sup>1a,5</sup> However, only fragmentary evidence supports this suggestion.<sup>6</sup> We report here the first systematic evidence for the dominant role of SOI in dictating the *endo/exo* product ratio of a DA reaction: that of cyclopropene with dienes.

Cyclopropene and many of its derivatives add to dienes with predominant *endo* selectivity.<sup>7</sup> A possible interpretation is in terms of SOI with the  $\pi_{CH_2}$  orbital of CP (Figure 1).<sup>4a</sup> Is this interpretation valid?

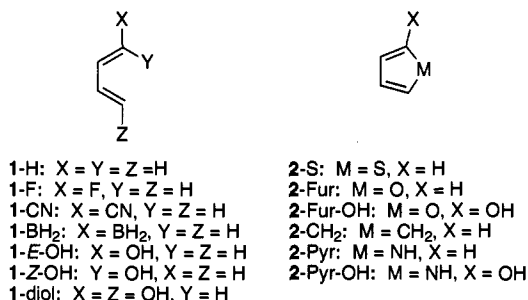
According to frontier molecular orbital (FMO) theory<sup>5,8</sup> the stabilization of the *endo* transition state due to SOI,  $\Delta E(\text{FMO})$ , is given by eq 2, where  $\Delta\epsilon$  is the energy gap between the

interacting frontier orbitals,  $c_1$  and  $c_2$  are the orbitals' coefficients, and  $\beta$  is the resonance integral.<sup>8</sup> Our hypothesis was

$$\Delta E(\text{FMO}) = (c_1 c_2 \beta)^2 / \Delta\epsilon \quad (2)$$

that if SOI control the stereochemistry, a correlation (ideally linear) should exist between  $\Delta E_a$ , the difference in the activation energies for *endo* and *exo* addition ( $\Delta E_a = E_a(\text{exo}) - E_a(\text{endo})$ ), and  $\Delta E(\text{FMO})$ .<sup>8</sup> Cyclopropene is an especially attractive dienophile for testing the importance of SOI because (1) its LUMO has a node at the methylene,<sup>8</sup> and consequently, of the two possible FMO interactions, only HOMO(CP) – LUMO-(diene) affects  $\Delta E(\text{FMO})$  (Figure 1); (2) the dipole moment of CP is relatively small,<sup>9</sup> minimizing other electronic effects, e.g., dipolar interactions; and (3) steric effects are relatively small.

Ab initio molecular orbital theory<sup>10</sup> was used to test whether a correlation exists between  $\Delta E_a$  and  $\Delta E(\text{FMO})$ . The transition states (TS) for *endo* and *exo* addition of CP to a series of substituted butadienes **1** and aromatic heterocycles **2** were fully characterized at RHF//3-21G.<sup>10</sup> Single-point calculations at the correlated MP2/6-31G\*//3-21G level<sup>10</sup> were used for energy comparisons. The reliability of this procedure is supported by the findings that optimization of the TS for the reactions of CP with **1-H** and **2-Fur** at MP2/6-31G\* resulted in small changes in  $\Delta E_a$ .<sup>11</sup>



For the limited available experimental data, i.e., the reactions of CP with butadiene (**1-H**),<sup>7g</sup> 1(*E*)-methoxybutadiene (**1**, X = OCH<sub>3</sub>, Y = Z = H),<sup>7f</sup> cyclopentadiene (**2-CH<sub>2</sub>**),<sup>7b</sup> and furan (**2-Fur**),<sup>7d,12</sup> the calculated  $\Delta E_a$  values agree nicely with the experimental *endo/exo* product ratios (Table 1), but the calculations slightly underestimate (by ca. 0.5–1 kcal/mol) the stability of the *endo* TS relative to the *exo* TS. Similar small destabilizations of the *endo* TS were reported for other DA reactions.<sup>13</sup>

The calculated Mulliken overlap populations (MOPs) at the *endo* TS (Table 1) show significant bonding overlap between

(7) (a) Review: Halton, B.; Banwell, M. G. *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: New York, 1987; Chapter 21. (b) Wiberg, K. B.; Bartly, W. J. *J. Am. Chem. Soc.* **1960**, *82*, 6375 (only the *endo* product was reported). (c) Lossing, P.; Semuluk, G. P. *Can. J. Chem.* **1970**, *48*, 955. (d) Trost, B. M.; Laroschelle, R. W. *J. Chem. Soc., Chem. Commun.* **1970**, 1353. (e) Plemenkov, V. V.; Breus, V. A. *Zh. Org. Khim.* **1974**, *10*, 1656. (f) Apeloig, Y.; Arad, D.; Kapon, M.; Wallerstein, M. *Tetrahedron Lett.* **1987**, 5917 (>95% *endo* product was reported). (g) Baldwin, J. E.; Reddy, V. P. *J. Org. Chem.* **1989**, *54*, 5264 (only the *endo* product was observed by NMR).

(8) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1976.

(9) Wiberg, K. B. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: New York, 1987; Chapter 1, pp 1–26.

(10) (a) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986. (b) Gaussian 92, Revision A: Frisch, M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Repolge, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A.; Gaussian Inc., Pittsburgh, PA, 1992.

(11) The changes in the intermolecular distances at the TS might be substantial; e.g., in the *endo* TSs: for (CP + **1-H**),  $r(C_1-C_1')$  = 2.28 Å (3-21G), 2.41 Å (MP2/6-31G\*); however, for (CP + **2-Fur**),  $r(C_1-C_1')$  = 2.21 Å (3-21G), 2.22 Å (MP2/6-31G\*).

† This paper is dedicated to Professor Paul von Ragué Schleyer on the occasion of his 65th birthday.

(1) (a) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1990; p 842–852 and references therein. (b) Alder, K.; Stein, G. *Angew. Chem.* **1937**, *50*, 510.

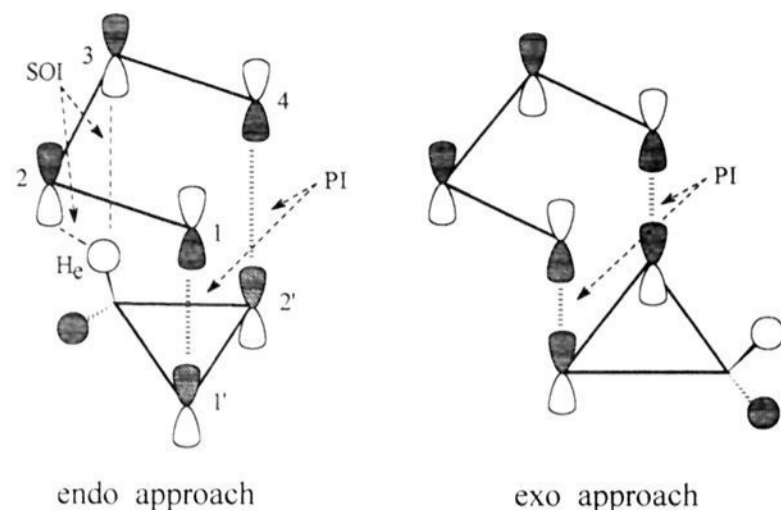
(2) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Verlag Chemie: Weinheim, 1971.

(3) Jorgensen, W. L.; Salem, L. *The Organic Chemist's Book of orbitals*; Academic Press, 1973.

(4) (a) Plemenkov, V. V.; Breus, V. A.; Grechkin, A. N.; Novikova, L. *K. Zh. Org. Khim.* **1976**, *12*, 787. (b) Sustmann, R.; Binsch, G. *Mol. Phys.* **1971**, *20*, 9.

(5) See, for example: Gilchrist, T. L.; Storr, R. C. *Organic Reactions and Orbital Symmetry*, 2nd ed.; Cambridge University Press: Cambridge, 1979.

(6) (a) Review: Ginsburg, D. *Tetrahedron* **1983**, *39*, 2095–2135. (b) Fox, A. M.; Cardona, R.; Kiweit, N. J. *J. Org. Chem.* **1987**, *52*, 1469. (c) Sustman, R.; Sicking, W. *Tetrahedron* **1992**, *48*, 10293. (d) Karcher, T.; Sicking, W.; Sauer, J.; Sustmann, R. *Tetrahedron Lett.* **1992**, *33*, 8027.



**Figure 1.** Schematic representation of primary (PI) and secondary orbital interactions (SOI) in the cycloaddition of cyclopropene to butadiene.

**Table 1.** Calculated and Experimental Energy Differences between *Exo* and *Endo* Transition States,  $\Delta E_a$ , in the Diels–Alder Reaction of Cyclopropene with Dienes **1** and **2**, the Calculated LUMO Energies of the Dienes, and the Calculated Mulliken Overlap Populations (MOP) at the *Endo* Transition States

entry	diene	$\Delta E_a(\text{exo-endo})$ , kcal/mol			LUMO, <sup>c</sup> eV	MOP, <sup>d</sup> $\times 10^3$
		3-21G	MP2/6-31G* <sup>a</sup>	exp <sup>b</sup>		
1	1-BH <sub>2</sub>	3.50	4.05		1.86	15.1
2	1-CN	2.80	3.45		2.17	14.2
3	2-S	2.70	3.20		3.63	11.7
4	1-F	2.03	2.90		3.78	12.0
5	1-H	2.44	3.10 (2.85) <sup>e</sup>	> 3.0 <sup>f</sup>	3.78	13.1
6	2-CH <sub>2</sub>	4.80	4.90	> 3.0 <sup>g</sup>	3.94	10.9
7	1-Z-OH	1.60	1.90		3.94	12.6
8	1-E-OH	0.50	1.40	> 2.5 <sup>h</sup>	4.12	11.5
9	1-diol	-1.53	0.36		4.59	10.0
10	2-Fur	-1.20	-0.40 (-0.54) <sup>e</sup>	+0.40 <sup>i</sup>	4.69	10.1
11	2-Fur-OH	-3.16	-1.40		5.06	8.5
12	2-Pyr	-1.85	-0.82		5.65	9.6
13	2-Pyr-OH	-1.57	-0.85		5.89	8.5

<sup>a</sup> 3-21G optimized geometries. <sup>b</sup> Calculated from the observed *endo/exo* product ratios. <sup>c</sup> At MP2/6-31G\*//3-21G, for the *s-cis* conformation. <sup>d</sup> Between H<sub>c</sub>-C<sub>2</sub> (or C<sub>3</sub>) in the *endo* TS. In unsymmetrical cases the average values are reported. <sup>e</sup> At MP2/6-31G\*//MP2/6-31G\*. <sup>f</sup> From ref 7g. <sup>g</sup> From ref 7b. <sup>h</sup> For the reaction of CP with 1(*E*)-methoxybutadiene.<sup>7i</sup> 1-*E*-OH is used as the computational model. <sup>i</sup> See footnote 12.

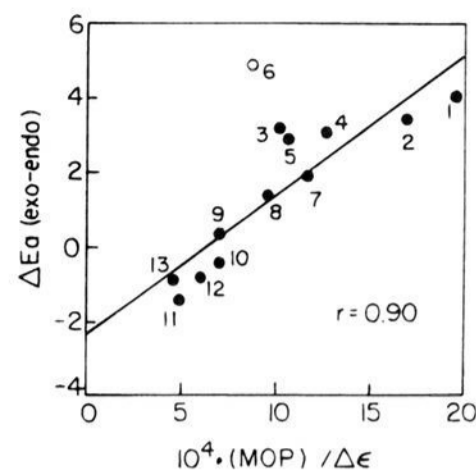
the *endo* methylenic hydrogen of CP (H<sub>c</sub>) and the diene's backbone carbons (C<sub>2</sub> and C<sub>3</sub>) (Figure 1), as expected if SOI are important.<sup>14</sup>

The calculated  $\Delta E_a(\text{exo-endo})$  values (Table 1) are linearly correlated with  $(\text{MOP})^2/[\text{LUMO}(\text{diene}) - \text{HOMO}(\text{CP})]$ , this term being proportional to  $\Delta E(\text{FMO})$ <sup>15</sup> (Figure 2,  $r = 0.90$ ), as expected if the stereochemistry of these reactions is controlled

(12) Being the *only* known DA reaction of CP were *both* isomers are observed, it was restudied, yielding in our hands an *endo/exo* product ratio of 2/1, in variance with the previously reported ratio of 1/1.<sup>7d</sup> We believe that the difference results from the fact that the NMR signals assigned previously<sup>7d</sup> to the *exo* DA adduct overlap (using a 60 MHz instrument which was probably used in the previous analysis,<sup>7d</sup> but not with a 200 MHz instrument) with signals belonging to an additional product, the *exo* adduct of the DA reaction between furan and the "ene-dimer" of CP. The latter product was not identified previously,<sup>7d</sup> and its NMR signals were erroneously assigned to the *exo* adduct of CP + butadiene.

(13) (a) Houk, K. N.; Loncharich, R. J.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1989**, *111*, 9172. (b) Jorgensen, W. L.; Lim, D.; Blake, J. F. *Ibid.* **1993**, *115*, 2936. (c) Houk, K. N.; Li, Y.; Evanseck, J. D. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 682.

(14) Birney, D. M.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 4127.



**Figure 2.** Plot of the calculated  $\Delta E_a(\text{exo-endo})$  at MP2/6-31G\*//3-21G vs  $\Delta E(\text{FMO}) = (\text{MOP})^2/[\text{LUMO}(\text{diene}) - \text{HOMO}(\text{CP})]$ , where MOP = Mulliken overlap population (see text).  $\Delta E_a$  is given in kcal/mol and  $\Delta\epsilon$  in eV. The numbering of points refers to the entries in Table 1.

by SOI. The *endo/exo* product ratio is higher for dienes with lower LUMOs and when the H<sub>c</sub>-C<sub>2</sub> (or H<sub>c</sub>-C<sub>3</sub>) overlap population is higher. The highest *endo* preference of 4.05 kcal/mol (i.e., an *endo/exo* product ratio of ca. 1000 at 27 °C) is calculated for 1-BH<sub>2</sub>, while preference for *exo* adducts is predicted for the furans (2-Fur and 2-Fur-OH) and the pyrroles (2-Pyr and 2-Pyr-OH).<sup>16</sup> The fact that the linear correlation in Figure 2 is not followed more closely is expected, considering contributions of effects other than SOI and the FMO assumptions, in particular the use of ground-state properties (i.e.,  $\Delta\epsilon$ ) to model the TS. Other correlations which are widely used to demonstrate that FMO interactions control chemical reactions exhibit similar or even lower correlation coefficients<sup>5,8</sup> than in Figure 2.

The reaction of CP and cyclopentadiene (empty circle in Figure 2) deviates strongly from the correlation line. The calculated  $\Delta E_a$  is larger by ca. 2.5 kcal/mol than expected from  $\Delta E(\text{FMO})$ . This deviation results from the strong steric repulsions in the *exo* TS between the methylenes of CP and cyclopentadiene, thus favoring the *endo* TS (by 2.5 kcal/mol) more than expected from eq 2.

To the best of our knowledge this study provides the first<sup>6</sup> systematic and quantitative evidence supporting the suggestion that SOI control the stereochemistry of a Diels–Alder reaction.<sup>17</sup> Is CP unique due to its special structure, which places one hydrogen close to both C<sub>2</sub> and C<sub>3</sub> of the diene, allowing efficient overlap? We believe that SOI play an important role also in other DA reactions, but systematic studies of the type described here are needed to establish this hypothesis.<sup>18</sup>

**Acknowledgment.** We thank Prof. S. Shaik for helpful discussions and the Fund for the Promotion of Research at the Technion for support.

JA950170P

(15) This is justified as follows: the MOP is given by  $2P_{\mu\nu}S_{\mu\nu}$ . However,  $P_{\mu\nu} = 2\sum C_{\mu}^*C_{\nu}$  (ref 10a, pp 21–28) and  $S_{\mu\nu}$  is proportional to  $\beta$ .<sup>8</sup>

(16) The intercept of the line in Figure 2 at -2.4 kcal/mol gives the predicted  $\Delta E_a(\text{exo-endo})$  in the absence of SOI (corresponding to an *exo/endo* product ratio of 54/1 at 27 °C); i.e., it measures mainly the difference in steric interactions in the two TSs.

(17) The interesting suggestion that the *endo/exo* stereoselectivity is determined by differences in  $\pi$ -orbital overlap at the *primary* centers (Hernedon, W. C.; Hall, L. L. *Tetrahedron Lett.* **1967**, 3095) is not supported by our calculations.

(18) SOI probably play a minor role in the dimerization of butadiene. See: Klärner, F. G.; Krawczyk, B.; Ruster, V.; Reiters, U. K. *J. Am. Chem. Soc.* **1994**, *116*, 7646. Li, Y.; Houk, K. N. *Ibid.* **1993**, *115*, 7478. However, this is not necessarily the case when the HOMO–LUMO gap is smaller than in butadiene.