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Steric Effects vs. Secondary Orbital Overlap in Diels–Alder Reactions. MNDO and AM1 Studies

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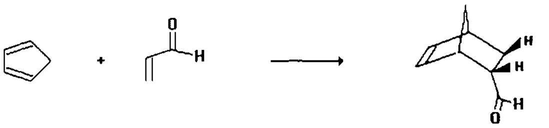
The importance of secondary orbital overlap in the Diels–Alder reaction of fulvene with cyclopentene or maleic anhydride has been examined by MNDO and AM1 semiempirical calculations. A comparison is made with the analogous reaction of cyclopentadiene with pentene or with itself. In these systems, steric effects are at least as important as secondary orbital interactions in controlling stereochemistry.

The goal of establishing those factors that control the regiochemistry and stereochemistry of reactions has challenged the organic chemist for many years. Many examples are known in which endo adducts are formed preferentially in Diels–Alder reactions conducted under kinetic control, e.g., eq 1–4.[1–3] Woodward and Hoffmann proposed secondary orbital overlap (SOO) as a molecular orbital based explanation of the observed endo stereopreference in the Diels–Alder reaction.[4]



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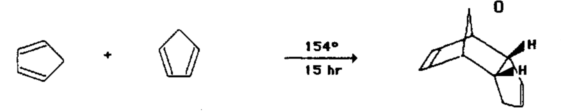

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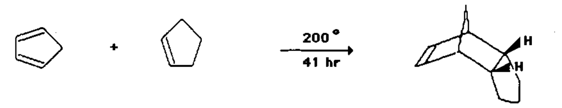

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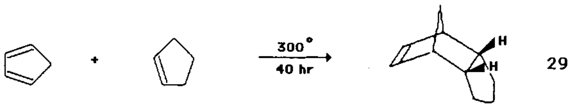
SOO is defined as the positive overlap of a nonactive frame in the frontier molecular orbitals of a pericyclic reaction. For example, in the Diels–Alder dimerization of butadiene, the primary interactions involve carbons 1–5 and 4–6 (Figure 1) and define the active frame where bonds are formed or broken. Carbons 3 and 7 are involved in a secondary interaction since no bond changes are encountered at these sites. These carbon atoms interact strongly in the endo transition state (Figure 2) but not at all in the exo transition state (Figure 3). Irrespective of whether the highest occupied molecular orbital (HOMO) of the diene interacts with the lowest unoccupied molecular orbital (LUMO) of the dienophile (Figure 2) or the diene LUMO interacts with the dienophile HOMO (Figure 4), orbital phasing at both the primary and secondary centers predicts a stabilizing interaction. SOO thus preferentially facilitates formation of the endo transition state compared with the exo transition state where such interaction is absent. This orbital argument does not, however, establish the magnitude of this stabilizing interaction, nor does it address its importance relative to other intermolecular interactions in the transition state.

Although the observed preference for endo adducts can be explained reasonably by secondary orbital overlap,[4,5] several striking examples, both experimental and calculational, show that other factors must also influence the observed stereopreference.[3,6–8] For instance, SOO cannot explain the endo preference in the addition of cyclopentene to cyclopentadiene, (eq 4)[3] since no secondary interactive sites are present.

That this stereopreference for endo adduct formation between cyclopentene and cyclopentadiene is kinetic rather than thermodynamic can be seen in the shift toward more exo product when the reaction is conducted under equilibrating conditions (c.f., eq 4 and 5). Despite the absence of a conceivable orbital basis for this kinetic acceleration, steric interactions do differ in the two transition states leading to the endo and exo products. If unfavorable steric interaction of the methylene group occurs in the exo transition state, as is possible in eq 1–4, such effects might provide a sufficient explanation for the observed stereoselectivity.



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It is the purpose of this work to evaluate the relative importance of steric interactions and SOO with semiempirical calculational methods. By use of MNDO[9] and AM1,[10] Diels–Alder adducts **1**, **3**, **5**, and **7** were compared to adducts **2**, **4**, **6**, and **8** to determine the relative importance of SOO stabilization of endo transition states and steric destabilization of exo transition states.

Results

MNDO and AM1 have been used for calculating the reaction pathways of the retro-Diels–Alder reactions of **1**–**8**. If one assumes that the retro-Diels–Alder reaction proceeds in a concerted synchronous fashion,[11] its progress can be

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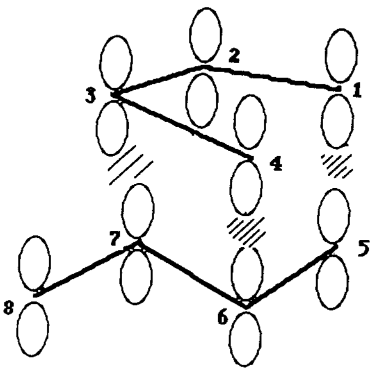


Figure 1. Primary and secondary orbital interactions in the Diels–Alder reaction.

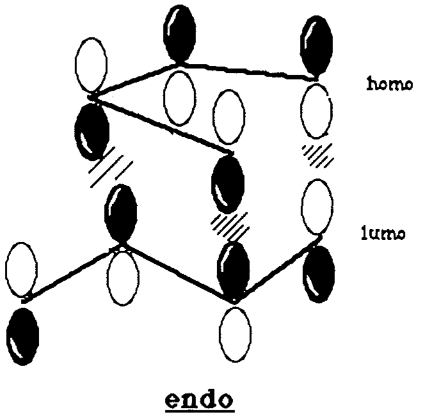


Figure 2. Frontier orbital interactions in the endo transition state of a Diels–Alder reaction: diene HOMO and dienophile LUMO.

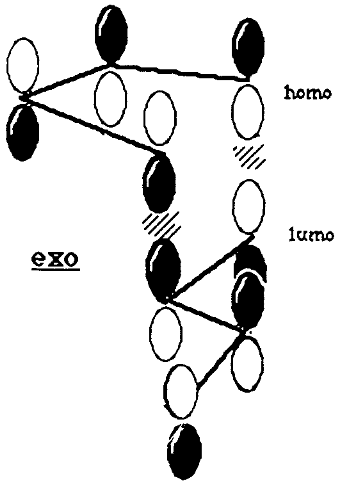


Figure 3. Frontier orbital interactions in the exo transition state of a Diels–Alder reaction.

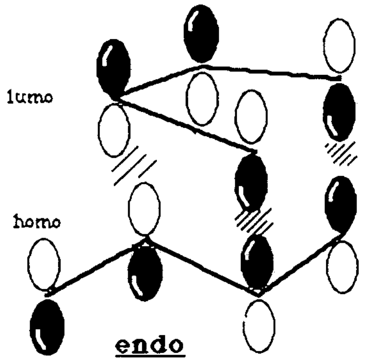
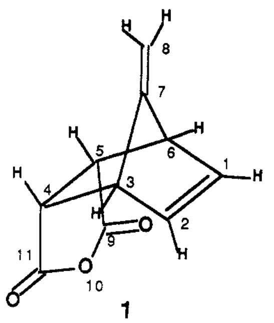


Figure 4. Frontier orbital interactions in the endo transition state of a Diels–Alder reaction: diene LUMO and dienophile HOMO.



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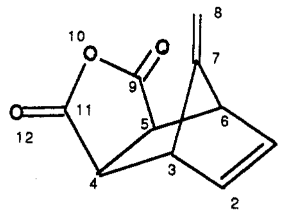

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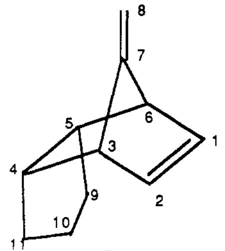

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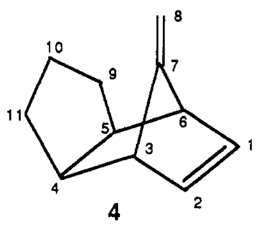

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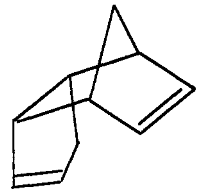

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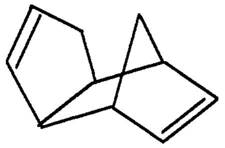

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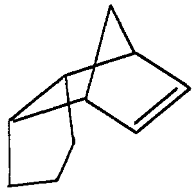

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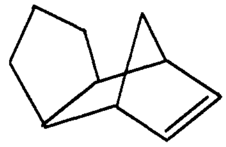

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followed by symmetrically elongating the bonds between carbons 3 and 4 and 5 and 6 and by following the energy and geometry changes as the bonds are broken. The geometry and heat of formation of the transition state were optimized in the usual fashion. Microscopic reversibility will then dictate an identical reaction pathway for the foward Diels–Alder reaction. Parallel results were obtained with each calculational technique, with slightly higher heats of formation having been obtained with the AM1 program. These small differences can be explained by slight underestimation of electron repulsion by MNDO, and the results reported here are those obtained by AM1 (Table I). Although the calculated transition-state energies for the retro-Diels–Alder reactions of **5** and **6** differ appreciably from the experimental values,[21] the calculated

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Table I. AM1 Calculated Activation Enthalpies for the Several Diels-Alder and Retro-Diels-Alder Reactions[a]

adduct	D-A: $\Delta H^{\ddagger}$, kcal/mol	retro-D-A: $\Delta H^{\ddagger}$, kcal/mol	exptl
1	54.5	73.9	
2	54.5	74.6	
3	64.2	74.9	
4	63.8	75.7	
5	63.9	64.8	(33.0)[21]
6	64.2	66.9	(37.4)[21]
7	65.8	63.9	
8	66.6	66.0	

[a] Calculated heats of formation: cyclopentadiene, 32.0; cyclopentane, −0.4; maleic anhydride, −88.7; fulvene, 53.6 kcal/mol.

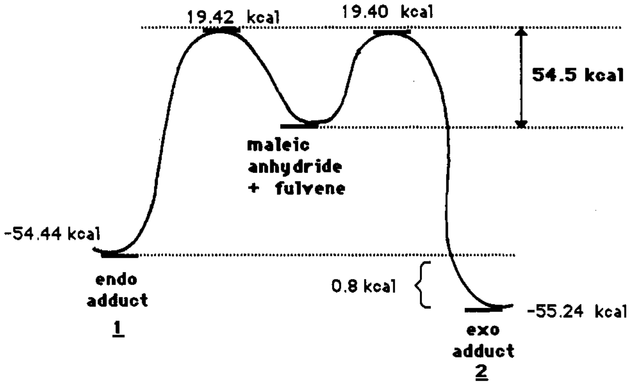

Figure 5. Calculated heats of formation and transition-state enthalpies for the retro-Diels–Alder reaction of the endo and exo adducts of fulvene and maleic anhydride.

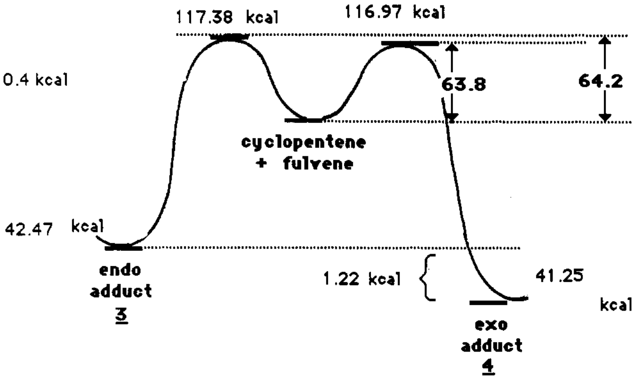

Figure 6. Calculated heats of formation and transition-state enthalpies for the retro-Diels–Alder reaction of the endo and exo adducts of fulvene and cyclopentene.

energetic ordering (i.e., the energy difference) of the exo and endo transition states agrees (within 2 kcal/mol) with experiment. The absolute error may have been caused by our imposition of synchronicity or by other systematic error in the series.

In the absence of a cyclopentadienyl CH$_2$ group, e.g., in the reaction of fulvene with maleic anhydride or cyclopentene, the energy of the endo and exo transition states are nearly identical (Figures 5 and 6), with a small, probably negligible, preference for the exo transition states. In the presence of this methylene group, e.g., in the reaction of cyclopentadiene with cyclopentene or with itself (Figures 7 and 8), the endo transition state lies about 1 kcal/mol lower in energy than the exo transition state, predicting, in agreement with experimental results, a kinetic preference for the endo product. In contrast to these kinetic effects, we find, from calculated heats of formation, the exo adduct to be thermodynamically more stable (again by about 1 kcal/mol) in all cases.

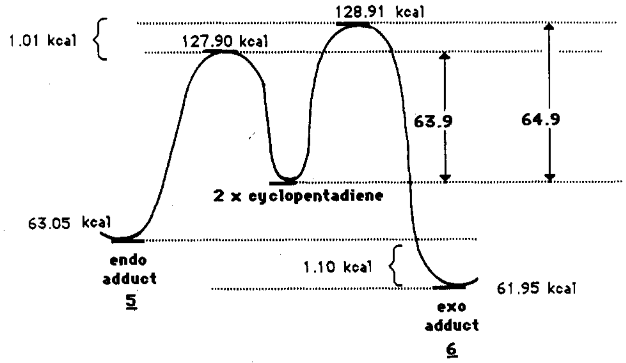

Figure 7. Calculated heats of formation and transition-state enthalpies for the retro-Diels–Alder reaction of the endo and exo adducts of cyclopentadiene dimerization.

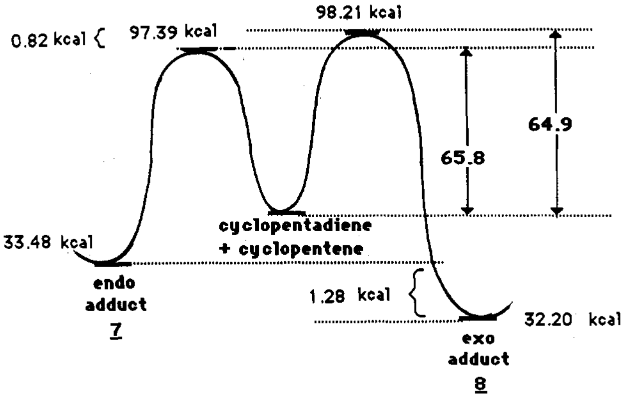

Figure 8. Calculated heats of formation and transition-state enthalpies for the retro-Diels–Alder reaction of the endo and exo adducts of cyclopentadiene and cyclopentene.

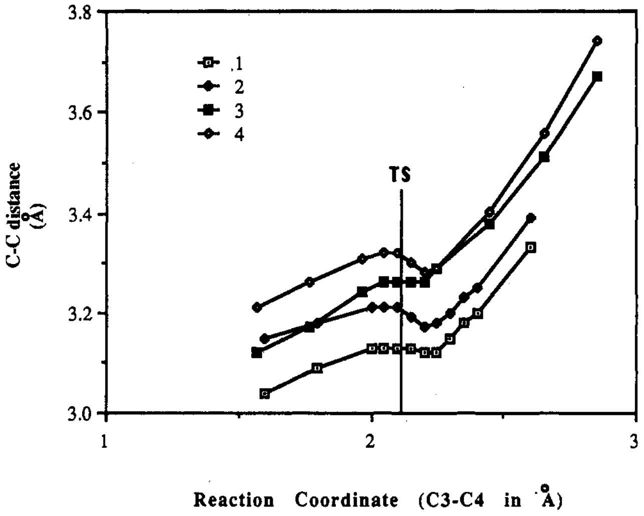

Figure 9. Reaction paths calculated near the transition states for the retro-Diels–Alder reactions of endo adducts 1 and 3 and for exo adduct 2. The *y* axis represents the distance between carbons 1 and 9 for the endo adducts 1 and 3 and between 7 and 9 for the exo adducts 2 and 4. Vertical line superimposed over the curve indicates transition-state geometries for each reaction.

When the distance between carbons 1 and 9 in the endo adduct 1 is plotted against the reaction coordinate (the C3–C4 distance), a steady separation is maintained through those distances closest to the transition state (ca. 2.15 ± 0.5 Å, Figure 9). A more pronounced energy minima is observed for the reaction pathway of 2, when carbons 7

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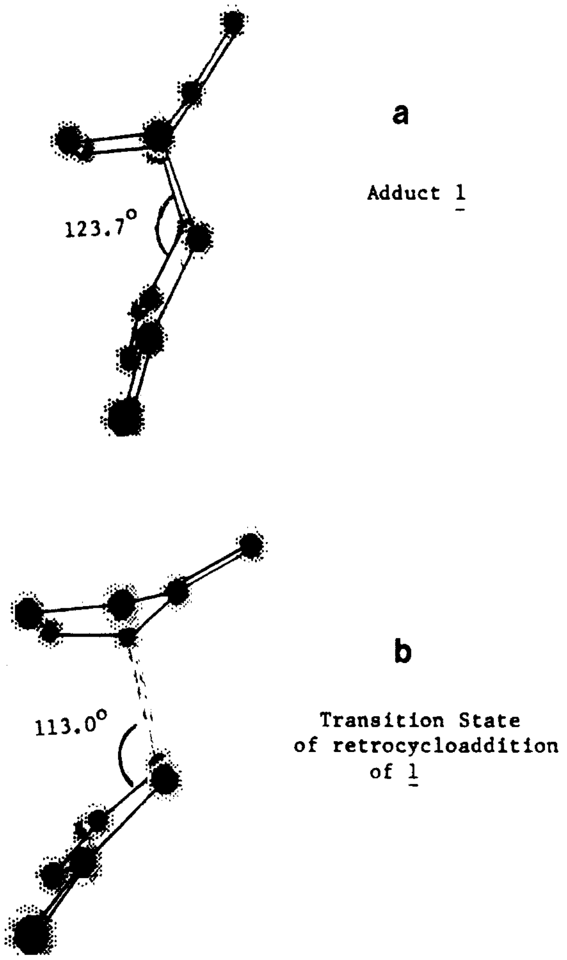


Figure 10. Three-dimensional views of dihedral angles in the retro-Diels–Alder reaction of 1: (a) ground state; (b) transition state.

and 9 are considered. Similar behavior is found for other members of the series **3–8**, with more pronounced geometry changes being encountered near the transition states for exo adduct formation.

Geometry changes encountered in moving from the ground state to the transition state are shown in Figure 10 for the endo adduct **1** and in Figure 11 for the exo adduct **2** (only the carbon skeleton is shown for clarity). The carbon skeleton of the incipient dienophile is roughly confined to a plane, rotation of which is measured by the dihedral angle at C-9 (9, 5, 4, 3). The degree of inward rotation of the pseudoplane of the incipient dienophile in the retrocycloaddition, as evidenced by a decrease in this dihedral angle, measures steric interaction as optimum π-alignment is attained. Table II lists the changes in dihedral angle (Δ_d) encountered upon moving from the ground state to the transition state for **1–8** and compares the difference in dihedral angle change with the calculated difference in transition energy for the endo and exo adducts.

Since the energy separation between the interacting frontier molecular orbitals determines the magnitude of interaction at both the primary and secondary sites, the HOMO–LUMO energy separation of some relevant dienes and dienophiles were calculated (Table III).

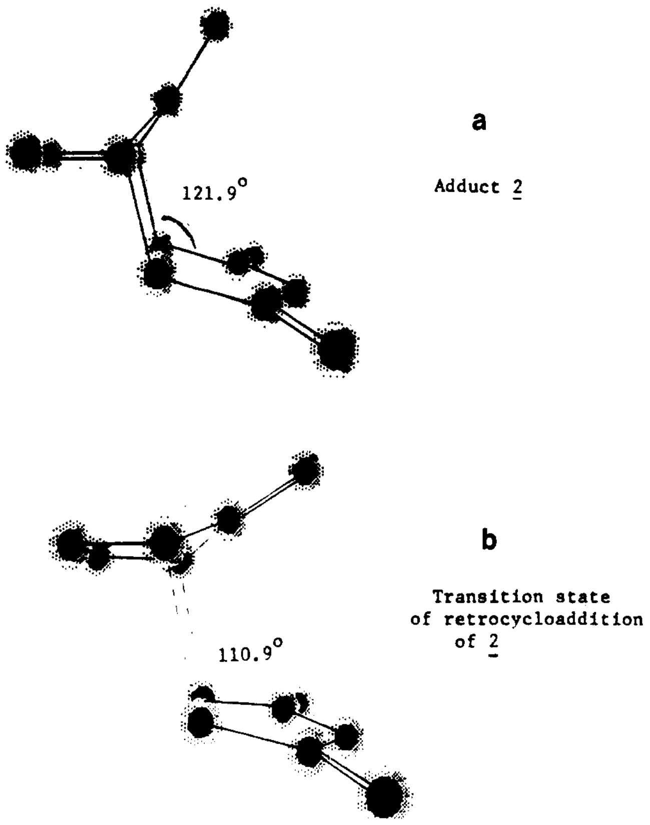


Figure 11. Three-dimensional views of dihedral angles in the retro-Diels–Alder reaction of 2: (a) ground state; (b) transition state.

Table II. Dihedral Angle Differences (Δ_d) between the Ground State and Transition States of Some Endo and Exo Diels–Alder Adducts

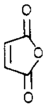
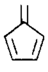
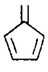
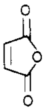
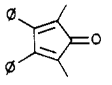
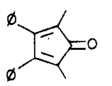
	dihedral angles, deg				
molecule	ground state	transition state	Δ_d	$\Delta(\Delta_d)$ (endo–exo)	$\Delta(\Delta H^{\ddagger})$ (endo–exo)
1	123.7	113.0	10.7		
				−0.03	+0.02
2	121.9	110.9	11.0		
3	126.0	118.6	7.4		
				−1.6	+0.4
4	124.8	115.8	9.0		
5	126.1	116.9	9.2		
				+0.8	−1.01
6	123.9	115.4	8.4		
7	126.8	118.5	8.3		
				+1.23	−0.82
8	123.8	116.8	7.0		

Discussion

The contrasting stereochemistry observed in Diels–Alder reactions conducted under kinetic and thermodynamic control implies the existence of some rate factor either favoring the endo or disfavoring the exo transition state (TS). Secondary orbital overlap has been invoked as a possible effect favoring the endo TS, while unfavorable steric interactions have been suggested as disfavoring the exo TS. Since it is very difficult to differentiate orbital and steric effects, the importance of SOO has remained controversial.

The addition of dienophiles to fulvene[12,17] or furan[13] generally gives rise to equilibrium-controlled product mixtures. In contrast, cyclopentadiene dimerization and the cycloaddition of cyclopentadiene to cyclopentene require extreme conditions in order to achieve equilibrium, so that the kinetic preference for endo adduct formation can be observed in most cases.[3] Since both SOO and steric factors are operative in the former reaction (eq 3) while only steric factors are operative in the latter transformation (eq 4), a complete theoretical description of these two reactions can, in principle, clarify the importance of SOO in stabilizing the kinetically favored endo transition state.

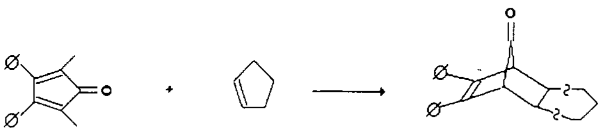
Table III. Lower Energy Gap between Frontier Molecular Orbitals of Reacting Partners

diene	dienophile	adduct from which derived	$E_{(\text{LUMO-HOMO})}$, eV
		7, 8	10
		5, 6	9.3
			7.5
		3, 4	9.3
			8.6
		1, 2	7.4
			7.7
			7.0

In particular, the importance of the C_5 methylenes of cyclopentadiene in tipping the balance toward the endo product can be evaluated.

If this methylene is absent (as in fulvene and furan), a mixture of products is formed rapidly; if the methylene is present, the endo isomer dominates even when no SOO is possible. If it can be assumed that the bulkier group will assume an endo site in the transition state, the preference for endo adduct formation can be explained without invoking SOO.[1,3] An alternate explanation of the "endo rule" proposed by Herndon[8] holds that the relatively stronger primary frontier orbital interaction encountered in the endo transition state is sufficient to justify the observed stereopreference.

Houk's ingenious attempt to differentiate these factors experimentally examined the reaction between a substituted cyclopentadienone and cyclopentadiene or cyclopentene (eq 6 and 7).[14] The presence of an extra double bond, allowing for the SOO, was found to transform the nonselective process (eq 6) into a stereoselective one (eq 7). The energy difference between the two transition states, presumably a measure of the importance of SOO, was 2.5–5.0 kcal/mol. In contrast to the results shown in eq 1–4 and 7, the addition of cyclopentene (eq 6) occurred in a nonstereoselective fashion when the methylenic group of the diene was removed.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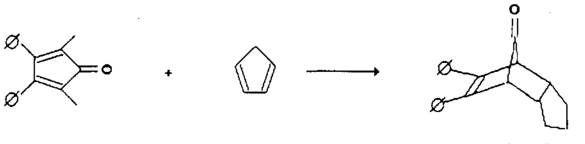
44:56 (endo:exo)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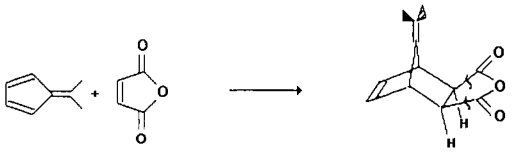
endo 97%

We have calculated the reaction pathways for the endo and exo adducts for the retro-Diels–Alder reactions of 1–8 in an effort to determine when steric factors become more important than SOO. Fulvene was chosen as the prototype for the reactions where the methylene is absent, in analogy to the substituted cyclopentadienone used by Houk but eliminating any possible interaction with oxygen. Since symmetrical reagents more closely approximate a concerted synchronous reaction pathway,[15,16] maleic anhydride (for 1 and 2) and cyclopentene (for 3 and 4) were chosen as the dienophiles.

As a model for reactions containing sterically inhibitory methylenes, cyclopentadiene was employed as dienophile, interacting either with itself (for 5 and 6) or with cyclopentene (for 7 and 8) as dienophiles.

The enthalpies of formation of the transition states (Figures 5 and 6) show hardly any difference between the exo and endo transition states when the methylene group is absent from the diene, i.e., in 1–4. This calculation is thus consistent with Craig and co-workers' report on the Diels–Alder reaction of 6,6-dimethylfulvene, where a 50:50 mixture of the endo and exo isomers is produced (eq 8).[17]


(8)

50:50 (endo:exo)

In the reactions with cyclopentadiene (Figures 7 and 8), however, calculation shows a small, but real, difference in transition-state energies. Thus, a stereorandom process is transformed into a stereoselective one upon introducing methylene steric interactions.

A second criterion for evaluating secondary interactions involves monitoring the distance, labeled as in 1 and 2, between carbons 1 and 9 for the endo isomer 1 (the relevant orbitals involved in secondary interactions) and between carbons 7 and 9 for the exo isomer 2 (the nearest analogous π–π orbitals) as the adduct proceeds along the reaction coordinate. Near the transition state, the C_1–C_9 distance remains nearly constant as the C_3–C_4 bond continues to elongate. Although this flattening might seem to indicate the existence of a favorable interaction maintaining a tight association of those atoms in the transition state (possibly SOO), an even greater effect is observed in 2, where no SOO can be involved. We assume therefore that this flattening of the bond distance near the transition state cannot be correctly interpreted as evidence for SOO, but rather as a π–π delocalization effect in the transition state. Similar behavior was observed for all the endo–exo pairs in the series.

A more informative factor was Δ_d, the change in the dihedral angle defined by carbons 9, 5, 4, and 3 in going from the ground state to the transition state (Table I). Δ_d is a measure of the extent of rotation of the pseudoplane of the incipient dienophile. Only a very small difference in dihedral angle change between the endo (Figure 10) and exo (Figure 11) isomers, $\Delta(\Delta_d)$, is found for the 1–2 pair. We interpret this nearly equal rotation to the absence of significant steric hindrance as the diene and dienophile approach the transition state. Furthermore, 1 and 2 showed the greatest absolute degree of rotation of this pseudo plane, about 11°. For example, 3 and 4 gave lower Δ_d's of 7.4° and 9.0°, respectively, indicative of a more crowded system, as might be expected from the presence of the C_9 hydrogens. In fact, we find a rough relationship between $\Delta(\Delta_d)$ and the number of hydrogens present to interact in the transition state with the noninteracting frame carbons (C1 and C2). Consistent with this idea we

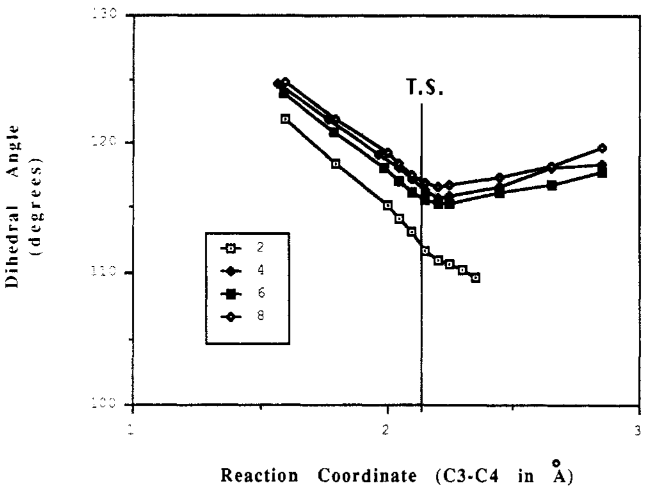


Figure 12. Changes in dihedral angle near the transition states for the retro-Diels–Alder reactions of exo adducts **2**, **4**, **6**, and **8**.

find positive $\Delta(\Delta_d)$ values, indicative of a sterically more hindered exo transition state, for those systems bearing diene methylenes (**5**/**6** and **7**/**8**) and negative $\Delta(\Delta_d)$ values for those systems lacking diene methylenes (**1**/**2** and **3**/**4**).

We also find a rough inverse correlation, both in sign and in magnitude, between $\Delta(\Delta_d)$ and $\Delta H^\ddagger$, the difference in energies of the endo and exo transition states. If $\Delta(\Delta_d)$ is a true representation of the degree of steric hindrance in the transition state, then it should correlate with $\Delta H^\ddagger$ only if steric interactions predominate over orbital effects is governing relative transition-state energies. That is, if stereoselectivity is controlled in these systems by a competition between steric effects and SOO, SOO should predominate only when steric effects are less significant.

The fact that the transition-state energies are nearly identical for **1** and **2**, the pair in which steric interactions are likely to be minimal, however, implies that any SOO stabilization of the endo TS must be offset by a parallel orbital stabilization of the exo transition state, by attractive steric interactions in the exo transition state[18] or by repulsive steric interactions in the endo transition state.[19] Of these, the first option is unlikely because in the HOMO of fulvene the exocyclic double bond is located at a node so that no possible HOMO–LUMO attractions can exist between the most proximate orbitals and the secondary orbitals of the maleic anhydride LUMO. The second option also seems unlikely since interactive π-centers are less likely candidates for significant attractive interactions than those described in the literature.[18] The latter option seems possible if closed-shell repulsion of the large exclusion shell accompanying heteroatoms is significant. Since this repulsion is likely to be small, however, so also must be the stabilizing effect of SOO. Presumably, then, the calculated differences for the other pairs (**3** and **4**, **5** and **6**, and **7** and **8**) can probably be explained by the more significant steric interactions at sp^3 hybridized atoms.

Figure 12 displays the change in dihedral angle near the transition state for the exo isomers **2**, **4**, **6**, and **8**. We note, first, that the break in slope occurs approximately at the transition state and, second, that the magnitude of the break parallels exactly the order of steric hindrance predicted for the pairs from Table II. (The top curve represents the sterically more hindered isomer and the bottom curve the less sterically hindered one.) The observed order of steric hindrance of these exo isomers can be attributed to the number of methylene interacting in the transition state (4, 3, 2, and 0 for **8**, **6**, **4**, and **2** respecively). A parallel plot of the endo isomers **1**, **3**, **5**, and **7** (Figure 13) shows a similar shape but with a less pronounced break, consistent with reduced steric sensitivity in the transition state. This attribution of stereoselectivity to steric effects has precedent in previous experimental investigations of Diels-Alder reactions.[20]

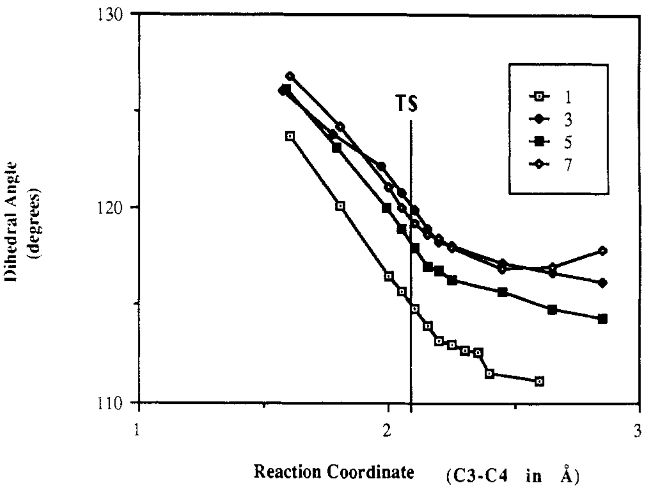


Figure 13. Changes in dihedral angle near the transition states for the retro-Diels–Alder reactions of endo adducts **1**, **3**, **5**, and **7**.

SOO is likely to be of greatest chemical consequence when the HOMO–LUMO separation is minimized. We note that for all systems examined here, except for fulvene/maleic anhydride, the gap is significantly larger than in Houk's stereoselective system. Since the stereoselectivity observed in cyclopentadienone/cyclopentadiene (eq 7) and cyclopentadiene/maleic anhydride (eq 2) is absent in dimethylfulvene/maleic anhydride (eq 8) and is predicted from our calculations to be absent in fulvene/cyclopentadiene, we conclude that a large HOMO–LUMO gap will allow for sufficient SOO to control stereoselectivity only when the relative importance of steric interactions is minimal. Consequently, the cyclopentadiene/maleic anhydride endo preference will be enforced by steric rather than electronic factors. Although SOO may indeed be the operative effect in cyclopentadienone/cyclopentadiene (eq 7), a significantly larger gap is encountered in our examples. We conclude, therefore, that the cause of the endo stereoselectivity in cyclopentadiene dimerization (eq 3, Figure 8) is probably steric rather than electronic.

Conclusions

1. The degree of endo stereoselection in several Diels–Alder reactions predicted from relative transition-state energies for endo and exo adduct formation obtained by MNDO and AM1 semiempirical calculations agrees with experimental results. Comparable results were obtained in each method.

2. For the retro-Diels-Alder reactions investigated here, the difference in the change in dihedral angle $\Delta(\Delta_d)$ of the endo and exo approaches of the incipient dienophile to the diene correlates with the difference in endo and exo transition-state energies. This correlation implies that steric effects are at least as important as secondary orbital effects in these systems.

3. For dienes bearing sterically interactive substituents, the normal endo stereopreference observed in Diels–Alder reactions is often caused by steric destabilization of the exo transition state.

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Registry No. Fulvene, 497-20-1; cyclopentene, 142-29-0; maleic anhydride, 108-31-6; cyclopentadiene, 542-92-7.