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Dienophile Twisting and Substituent Effects Influence Reaction Rates of Intramolecular Diels−Alder Cycloadditions: A DFT Study

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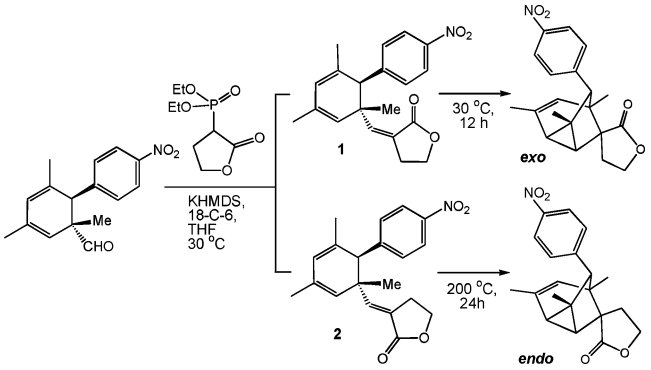
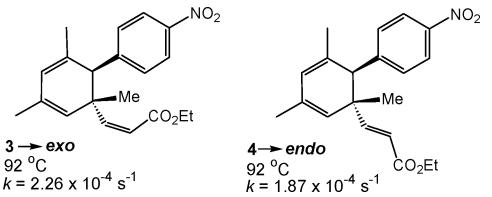
The *Z* and *E* isomers, **1** and **2**, of substituted 5-vinyl-1,3-cyclohexadienes exhibit remarkably different reactivities in intramolecular Diels−Alder reactions.[1] Whereas **1** cannot be isolated at 30 °C because it undergoes rapid cycloaddition to give the exo adduct, compound **2** requires a temperature of 200 °C to give the intramolecular endo adduct. Assuming that the reaction rate of **1** at 30 °C is equal to that of **2** at 200 °C, $\Delta G_2^{\ddagger}$ must be 1.4 times larger than $\Delta G_1^{\ddagger}$![2]



When the lactone is replaced by an acyclic ester, as in **3** and **4**, the rates of the exo and endo cycloadditions are similar, with the exo adduct being formed only slightly faster than the endo adduct.



B3LYP/6-31G(d) density functional calculations as implemented in *Gaussian 03*[3] were used to determine those factors that influence the relative rates of the exo/endo intramolecular cycloadditions of 5-vinyl-1,3-cyclohexadienes.

The activation enthalpy for the cycloaddition of 5-vinyl-1,3-cyclohexadiene is 30.1 kcal/mol. The TS (Figure 1) is nearly synchronous; the two forming σ-bonds (labeled A and B) are 2.08 and 2.11 Å in length and fall within the typical range of 1.86−2.40 Å for pericyclic transition structures.[4] *Z* substitution on the vinyl group leads to exo (*x*) placement in the TS, and *E* substitution leads to endo (*n*) placement. The position of the bridging $-CH_2-$ group in the TS is reminiscent of that observed for the intermolecular cycloadditions involving cyclopentadiene.

What distinguishes this intramolecular cycloaddition from typical cycloadditions is that nonparallel formation of two bonds forces the terminal end of the vinyl group to twist with respect to the internal terminus, destabilizing the π bond of the dienophile. The

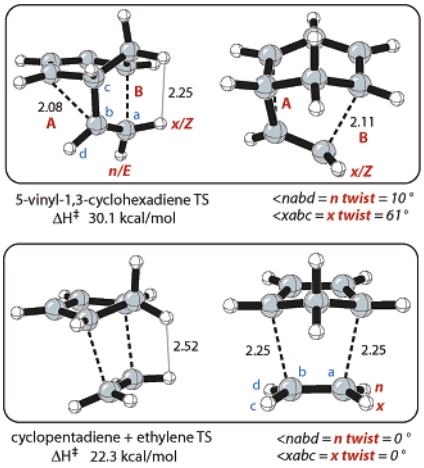


Figure 1. Two views of TSs for intra- and intermolecular Diels−Alder cycloadditions.

degree of twisting is quantified by measuring the cis dihedral angle containing either the exo substitutent (<*xabc* = *x* twist) or the endo substituent (<*nabd* = *n* twist). One consequence of the cycloaddition geometry is that the exo substituent must twist significantly more than the endo (61° versus 10°). In contrast, no twisting of the dienophile occurs in the intermolecular TS between cyclopentadiene and ethylene (<*xabc* = <*nabc* = 0°). The reluctance to twist in the intramolecular case causes the exo substituent to be very close to a methylene H (see Figure 1).

Results for the substituted vinylcyclohexadienes are compiled in Table 1. Entries 1−4 are model systems designed to examine how alkene substitution influences intramolecular reactivity. Four calculated enthalpies are recorded for each entry: the activation enthalpy of the exo system ($\Delta H_{exo}^{\ddagger}$), that of the endo system ($\Delta H_{endo}^{\ddagger}$), the enthalpy difference between the endo and exo reactants ($\Delta\Delta H_R$), and the enthalpy difference between the exo and endo transition structures ($\Delta\Delta H_{TS}$). Both $\Delta\Delta H_R$ and $\Delta\Delta H_{TS}$ are direct comparisons of the stabilities of isomeric species, allowing one to analyze whether reactant stability or TS stability is dominating the rate differences between isomeric pairs. The following conclusions can be drawn from Table 1.

The positive $\Delta\Delta H_R$ values indicate that the *Z* alkenes are always less stable than the corresponding *E* alkenes due to steric repulsion. The energetic penalty is slightly larger when an ester group rather than a methyl or methylene group is placed in the *Z* position. The additional methyl group (R = Me) included in entries 1b−4b significantly amplifies the steric congestion of the *Z* alkene and substantially lowers both endo and exo barriers.

The effect of alkene substitution on TS stability is best addressed by analyzing the $\Delta\Delta H_{TS}$ values. A methyl group prefers the endo position in the cycloaddition TS by 7.9 kcal/mol (entry 1); the ester prefers the endo position by 4.0 kcal/mol (entry 2). The endo

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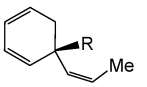
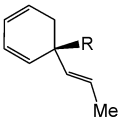
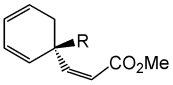
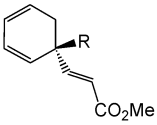
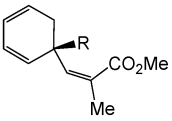
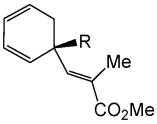
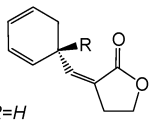
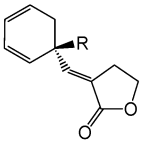
Table 1. B3LYP/6-31G(d) Activation Enthalpies at 298 K for Substituted Vinylcyclohexadienes ($\Delta H^{\ddagger}$)[a]

Entry	*exo / Z*	*endo / E*	$\Delta H^{\ddagger}$ *(exo)*	$\Delta H^{\ddagger}$ *(endo)*	$\Delta\Delta H_R$ *(x-n)*	$\Delta\Delta H_{TS}$ *(x-n)*
(1a)			37.1	30.9	1.7	7.9
(1b)			30.2	26.9	4.6	7.9
(2a)			31.5	29.4	1.9	4.0
(2b)			24.6	25.6	4.9	3.9
(3a)			31.3	35.9	0.8	-3.9
(3b)			23.2	30.7	3.4	-4.1
(4a)			28.8	34.9	0.5	-5.7
(4b)			21.6	30.3	3.0	-5.8

(a) R=H
(b) R=Me

[a] A direct comparison of exo/endo reactant enthalpies ($\Delta\Delta H_R$) and exo/endo TS enthalpies ($\Delta\Delta H_{TS}$) is also included. When the alkene is disubstituted at the terminal position, the electron-withdrawing group is used to designate endo or exo. Enthalpies are given in kilocalories per mole.

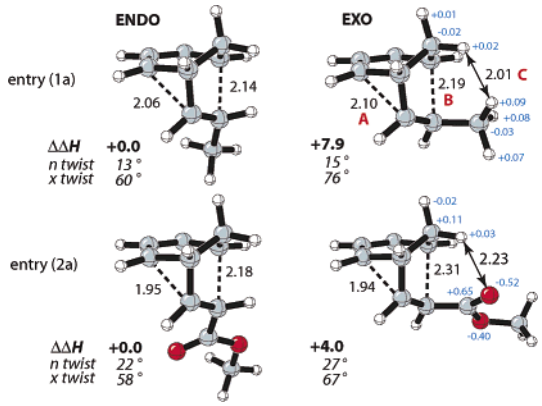


Figure 2. Endo and exo transition structures for Table 1, entries 1a and 2a. Enthalpies are given in kilocalories per mole, and bond lengths in angstroms. ChelpG charges are shown in blue.

preferences are much larger than those observed for the intermolecular cycloadditions of cyclopentadiene and propene (1.2 kcal/mol) or cyclopentadiene and methyl acrylate (0.6 kcal/mol).[5] Endo substitution in the intramolecular cases avoids steric repulsion with the bridging $-CH_2-$ group, whereas the exo substituent is still forced into a crowded environment despite alkene twisting (note distance C, Figure 2).

A comparison of the exo-methyl and exo-ester TSs reveals why methyl substitution leads to dramatically higher rate differences (Figure 2). The bulkier methyl group produces greater steric repulsion and greater loss of π conjugation in the exo TS. Also, the ester group favors a more asynchronous transition structure where bond A is more fully formed; as a result, twisting inflicts a smaller energetic penalty. Finally, a small favorable electrostatic interaction between the negatively charged ester oxygen and the positively charged $-CH_2-$ group is present when the ester is exo.

When both methyl and ester groups are present, as in entries 3 and 4, where 4 features a lactone, the large preference for an endo methyl is maintained, and the more stable TS has the endo methyl/exo ester combination. For entry 3, the TS substituent effects are approximately additive: the 7.9 kcal/mol preference for an endo methyl is balanced by a 4.0 kcal/mol penalty for an exo ester, and the predicted $\Delta\Delta H_{TS}$ is -3.9 kcal/mol. The geometric and electrostatic features observed in the monosubstituted TSs are also present in those that are disubstituted (Figure 3). Entry 4b, which closely corresponds to experimental compounds **1** and **2**, has endo and exo activation enthalpies that differ by a factor of 1.4, indicating that the model systems are sufficient for revealing the origins of stereoselectivity.

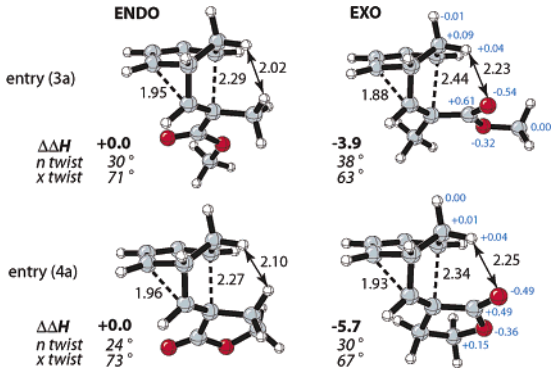


Figure 3. Endo and exo transition structures for Table 1, entries 3a and 4a. Enthalpies are given in kilocalories per mole, and bond lengths in angstroms. ChelpG charges are shown in blue.

The $\Delta\Delta H_{TS}$ of entry 4 is ~2 kcal/mol more negative than that of 3. We are currently in the process of determining whether the enhanced reactivity difference predicted for entry 4 versus entry 3 is related to the enhanced exo selectivity observed in intermolecular cycloadditions of methylene lactone versus methyl methacrylate.[6]

In conclusion, dienophile twisting is the feature of 5-vinyl-1,3-cyclohexadiene cycloadditions that accompanies the unusually severe steric demands for exo-substituted TSs. Compounds **3** and **4** have very similar cycloaddition rates because the reactant destabilization of *Z* isomer **3** is almost exactly balanced by the endo transition state stabilization of isomer **4**. On the other hand, compound **1** benefits from both reactant destabilization and transition state stabilization as compared to **2**, giving rise to the observed rate enhancement for the endo methylene/exo ester isomer.

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Supporting Information Available: B3LYP coordinates, electronic energies, enthalpies, free energies, and entropies of reactants and TSs in Table 1. Full authorship of ref 3. This material is available free of charge via the Internet at http://pubs.acs.org.

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