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Lewis Acid Catalysis Alters the Shapes and Products of Bis-Pericyclic Diels−Alder Transition States

Nihan Çelebi-Ölçüm,[†,‡] Daniel H. Ess,[‡] Viktorya Aviyente,[†] and K. N. Houk*[,‡]

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569, and Department of Chemistry, Boğaziçi University, Bebek, Istanbul 34342, Turkey

Received January 30, 2007; E-mail: houk@chem.ucla.edu

The discovery by Caramella et al.[1−4] that the dimerization of several dienes occurs by a single "bis-pericyclic" transition state leading to two products has prompted a flurry of activity to find other reactions with similar potential energy surfaces (PES) featuring reaction path bifurcations.[5−10] Figure 1 shows an idealized contour diagram for the Diels−Alder (DA) dimerization of butadiene. A reaction trajectory passing through TS1 follows a downhill intrinsic reaction coordinate (IRC) until it emerges from a valley onto a ridge (the valley−ridge inflection point, VRI).[11−15] In the vicinity of the VRI, the path bifurcates into two equivalent downhill pathways. The VRI occurs between TS1 and TS2, the Cope rearrangement transition state. We earlier studied the singlet oxygen ene reaction with Singleton and others and described this as a two-step no-intermediate mechanism.[7]

We have now discovered that competing DA reactions including two different dienes can have a very unsymmetrical bis-pericyclic transition state that leads predominantly to one of the possible products. The shape of the PES and the major product are both reversed by Lewis acid (LA) catalysts.

The reactions of cyclopentadiene (**Cp**) with α-keto-β,γ-unsaturated phosphonates (**1a**) or with nitroalkenes (**1b**) with and without Lewis acid catalysts were studied independently by Hanessian,[16] Evans,[17,18] and Denmark[19] (Scheme 1). **Cp** is well-known as an excellent 4π component in many Diels−Alder reactions due to its favorable geometrical features. Indeed, **Cp** behaves as expected toward dienophiles **1a** and **1b**, forming the major products **2a** and **2b** in the uncatalyzed reaction. Minor amounts of the hetero-Diels−Alder (HDA) cycloadducts **3a** and **3b** are formed, indicating that there is a competing reaction channel in which **Cp** acts as a dienophile. A reversal of periselectivity occurs in the presence of Lewis acid catalysts, such as $SnCl_4$; now the formation of HDA cycloadducts **3a** and **3b** is favored, and only minor amounts of the DA products **2a** and **2b** are formed.

The periselectivity of competing reactions is typically accounted for by the difference in barrier heights between two pericyclic addition channels as represented in Figure 2a. However, when these two distinct transition states merge into a single transition state, the preferential formation of one product is controlled by the branching ratio from a single unsymmetrical bis-pericyclic transition state leading to two distinguishable products as illustrated in Figure 2b,c. These differ from Figure 1 since the two products are no longer identical. The resulting asymmetric VRIs have been discussed by Quapp.[15b]

Calculations[20] with the B3LYP functional on the thermal reaction located only a single endo transition state for the DA cycloaddition of **Cp** with **1a** or **1b**.[21] Products **2a,b** are preferentially formed according to IRC calculations. No separate transition state could be located for the HDA reaction to form **3a,b**, and no energy barrier separates **3a,b** from the transition state. The geometries of the endo cycloaddition transition states (TS1) and Claisen rearrangement transition states (TS2) of **1a**+**Cp** are given in Figure 3a, and those of **1b**+**Cp** are in the Supporting Information. TS1 is highly asynchronous: the forming C···C bond between the ends of the diene system is more developed ($r_A = 1.99$ Å) than two other partial bonds ($r_B = 2.80$ Å and $r_C = 3.01$ Å). The transition state resembles an asynchronous DA transition state stabilized by the secondary orbital interaction (SOI) C as in Figure 2b. Calculations on a grid of 300 points to elucidate the topology of the PES reveal that the HDA product is also downhill from TS1 (see Supporting Information), so that the formation of the minor product can also occur from the bis-pericyclic transition state.

Despite the high asynchronicity and the zwitterionic character of TS1 (charge separation of 0.3e), the mechanism is still concerted,

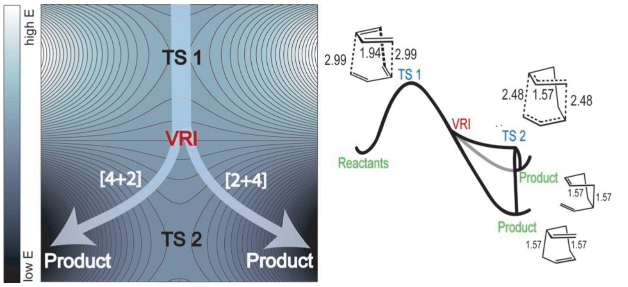
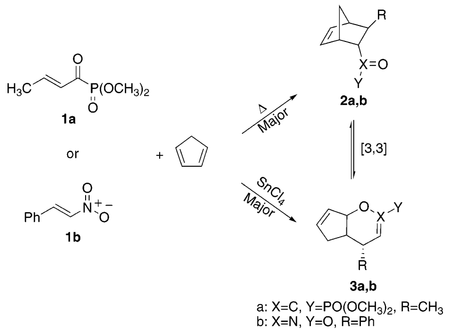


Figure 1. Idealized contour diagram for Diels−Alder dimerization of butadiene. The arrows represent trajectories, while the IRC connects VRI to TS2.

Scheme 1. Competing Diels−Alder and Hetero-Diels−Alder Reactions



a: X=C, Y=$PO(OCH_3)_2$, R=CH_3
b: X=N, Y=O, R=Ph

[‡] University of California, Los Angeles.
[†] Boğaziçi University.

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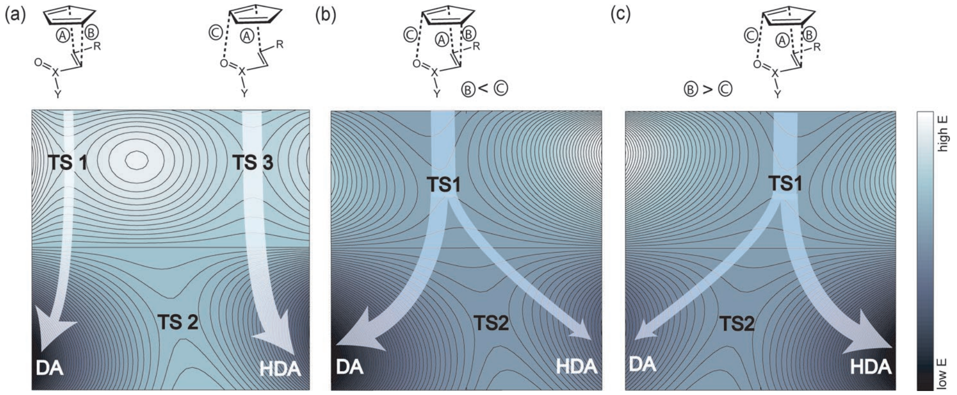

Figure 2. Idealized contour plot for (a) unsymmetrical potential energy surface with two different reaction channels. (b) Unsymmetrical bis-pericyclic potential energy surface leading mainly to Diels−Alder (DA) product. (c) Unsymmetrical bis-pericyclic potential energy surface leading mainly to hetero-Diels−Alder (HDA) product. The arrows are qualitative representations of probable reaction paths.

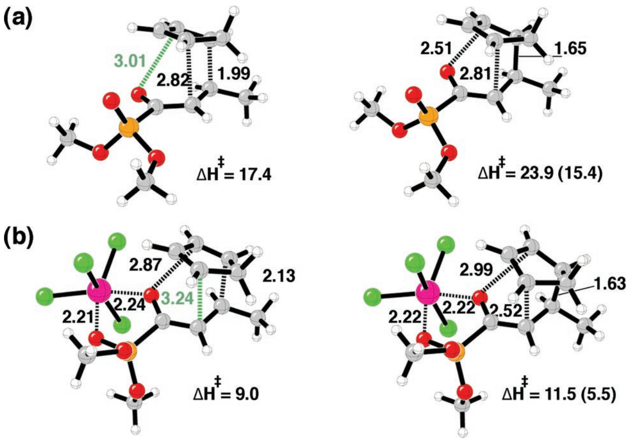

Figure 3. B3LYP/6-31+G(d) geometries of cycloaddition transition states (TS1) and [3,3]-sigmatropic shift transition states (TS2) (a) of the thermal reaction and (b) of $SnCl_4$-catalyzed reaction. The activation enthalpies are given in kcal/mol versus **Cp+1a** for TS1 and versus **2a** for TS2. The values in parentheses for TS2 are the relative enthalpies of the Claisen TS versus **Cp+1a**.

since no intermediate exists on the PES. TS2 is skewed in the opposite direction. As represented by the width of the arrows in Figure 2b, the bifurcation occurs to give mostly DA product, **2a,b**. TS1 and TS2 are close in energy ($\Delta\Delta H = 2$ kcal/mol), but their geometries differ substantially.

The endo transition state located for the $SnCl_4$-catalyzed reaction (Figure 3b) connects the reactants to both **3a,b** and **2a,b**. Bond C, leading to the HDA reaction, is shorter than the SOI, B ($r_C = 2.87$ Å and $r_B = 3.24$ Å). The Lewis acid has now shifted TS1 in one direction, and the Claisen rearrangement transition state, TS2, in the opposite direction. The charge transfer is larger due to the presence of Lewis acid (0.4e), but the mechanism is still concerted without any intermediates. The lowest unoccupied molecular orbital (LUMO) of **1a,b** and that of **1a,b·SnCl$_4$** are significantly different: coordination of the catalyst to **1a** or **1b** causes a significant decrease in the coefficient of the dienophile carbon adjacent to the ketophosphonate or nitro group and increases the carbonyl-O coefficient (see Supporting Information). This is consistent with the change in direction of the cycloaddition toward the HDA reaction.

Lewis acid catalysis modifies the positions and energetics of sequential transition states, changing the branching ratio of the two modes of cycloaddition. The experimental observations about competing Diels−Alder and hetero-Diels−Alder reactions and shifts in product ratios by acid catalysis can be understood from the single malleable bis-pericyclic transition state.

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Supporting Information Available: Cartesian coordinates and absolute energies of transition states, PES scan results, LUMO coefficients of dienophiles, and complete ref 20 are provided (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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