

Cycloadditions of Cyclopentadiene and Cycloheptatriene with Tropone: All *Endo*-[6+4] Cycloadditions Are AmbimodalCooper S. Jamieson,[†] Arkajyoti Sengupta,[†] and K. N. Houk*Cite This: *J. Am. Chem. Soc.* 2021, 143, 3918–3926

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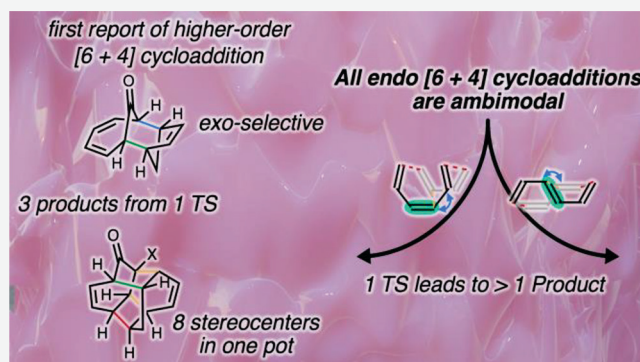


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ABSTRACT: The cycloadditions of cyclopentadiene and cycloheptatriene with tropone are some of the earliest published examples of [6+4] cycloaddition reactions. We report quantum mechanical studies (ω B97X-D and DLPNO-CCSD(T)) of transition structures and products of these reactions, as well as quasi-classical molecular dynamics simulations of reaction trajectories. The study reveals that these cycloadditions involve ambimodal transition states resulting in a web of products by pericyclic interconversion pathways. Combined with these studies, calculations of simple parent systems and a thorough meta-analysis of literature examples reveal the general concept that all *endo*-[6+4] cycloadditions are ambimodal.



■ INTRODUCTION

In 1965,¹ and in the full description of orbital symmetry selection rules in 1969,² Hoffmann and Woodward predicted that trienes and dienes could react in concerted [6+4] cycloadditions to give 10-membered-ring products. Later they predicted that this reaction should proceed with *exo*, rather than *endo*, stereochemistry due to repulsive secondary orbital interactions in the *endo* transition state (TS).³ These predictions were quickly confirmed by independent discoveries by the Cookson and Itô groups,^{4–6} both of which studied the reaction of cyclopentadiene and tropone (Figure 1A). The predictions were also verified in the Woodward laboratories with more heavily substituted reactants (Figure 1B).⁷

A variety of [6+4] cycloadditions have since been discovered,⁸ including some that are catalyzed by enzymes in nature.^{9–12} Among the earliest examples of [6+4] cycloadditions were the studies from the Itô group of the reactions of cycloheptatriene with tropone and several substituted tropones (Figure 1C).^{13–16} These cycloaddition cascades generate eight stereogenic centers to form a densely functionalized pentacyclic adduct. We have re-examined these reactions computationally with modern accurate density functional theory (DFT) and molecular dynamics simulations. These studies found a web of hidden processes occurring from ambimodal TSs. Revisiting these early examples of [6+4] cycloadditions revealed a striking and general phenomenon: all *endo*-[6+4] cycloadditions are ambimodal.

About 35 years after the first published [6+4] cycloaddition, the Caramella group discovered a bis-pericyclic TS in the computational investigation of cyclopentadiene dimerization.¹⁷ They showed that one TS could lead to multiple (in this case

two identical) pericyclic reaction products due to a post-transition-state bifurcation. Such reactions are now generally referred to as ambimodal reactions.^{18,19} This phenomenon occurs when a TS is connected without an intermediate to a second TS that is perpendicular to the reaction coordinate and interconverts the products. Caramella,²⁰ Singleton,^{21,22} Tantillo,^{19,23} and our group²⁴ have expanded on this concept, discovering TSs that can lead, after multiple bifurcations on the potential energy surface, to three²⁵ or more pericyclic reaction products. In this context, we hypothesized that the reaction of tropone and either cyclopentadiene or cycloheptatriene could also involve ambimodal TSs.

■ COMPUTATIONAL METHODS

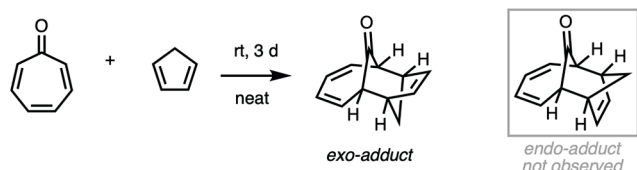
We have now explored these reactions with highly accurate DFT and wavefunction methods at the DLPNO-CCSD(T)/cc-pVQZ// ω B97X-D/def2-TZVP level of theory as implemented in ORCA 4.1.1 and Gaussian 16,^{26–33} and describe here the details of calculated reaction energetics of cyclopentadiene with tropone, and of cycloheptatriene with tropone and several substituted tropones. These studies depict the importance of secondary orbital interactions in controlling not only stereoselectivity but the periselectivity (selectivity between pericyclic reactions) of higher-order cycloadditions and elaborate on the generality of single pericyclic TSs that lead to multiple products.

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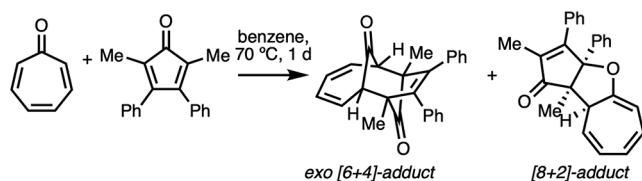
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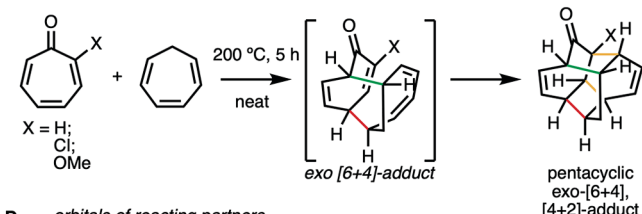
A 1966, 1970 – Cookson and Itô



B 1970 – Woodward and Houk



C 1967, 1969, 1975 – Itô



D orbitals of reacting partners

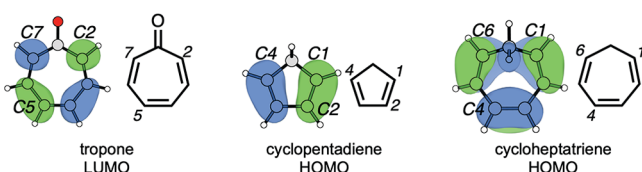


Figure 1. Early examples of higher-order [6+4] cycloadditions. (A) Independent studies by Cookson and Itô in 1966 and additionally reported in 1970. (B) Verification of Hoffmann and Woodward's prediction: tropone and cyclopentadiene react to form an *exo*-tricyclic adduct with π systems *anti* to each other (Figure 1A). Considering the frontier molecular orbitals (Figure 1D), the nucleophilic C1 of cyclopentadiene (highest occupied molecular orbital, HOMO) interacts with the electrophilic C2 of tropone (lowest unoccupied molecular orbital, LUMO) thus also connecting C4 of cyclopentadiene and C7 of tropone. When the π -systems are arranged *syn*—an *endo* orientation—there is an out-of-phase orbital interaction between C2 and C3 of cyclopentadiene and C3 and C6 of tropone that reduces stabilizing orbital interactions. In the *exo* orientation, when the π -systems are *anti*, there are no antibonding interactions. There can be a stabilizing secondary orbital interaction in the *exo* orientation between the tropone oxygen HOMO and C2 and C3 of the cyclopentadiene LUMO, although this is the weaker frontier MO interaction and has a small effect at most (Supplemental Figure S1). Strong secondary orbital interactions can become primary interactions and lead to bond formation; this is manifested in ambimodal reactions, where the TSs have orbital interactions that can lead to several products. Second, the related

RESULTS

Cyclopentadiene and Tropone: Frontier Molecular Orbitals. Cookson and Itô confirmed Hoffmann and Woodward's prediction: tropone and cyclopentadiene react to form an *exo*-tricyclic adduct with π systems *anti* to each other (Figure 1A). Considering the frontier molecular orbitals (Figure 1D), the nucleophilic C1 of cyclopentadiene (highest occupied molecular orbital, HOMO) interacts with the electrophilic C2 of tropone (lowest unoccupied molecular orbital, LUMO) thus also connecting C4 of cyclopentadiene and C7 of tropone. When the π -systems are arranged *syn*—an *endo* orientation—there is an out-of-phase orbital interaction between C2 and C3 of cyclopentadiene and C3 and C6 of tropone that reduces stabilizing orbital interactions. In the *exo* orientation, when the π -systems are *anti*, there are no antibonding interactions. There can be a stabilizing secondary orbital interaction in the *exo* orientation between the tropone oxygen HOMO and C2 and C3 of the cyclopentadiene LUMO, although this is the weaker frontier MO interaction and has a small effect at most (Supplemental Figure S1). Strong secondary orbital interactions can become primary interactions and lead to bond formation; this is manifested in ambimodal reactions, where the TSs have orbital interactions that can lead to several products. Second, the related

experimental findings by Houk and Woodward showed that substituted cyclopentadienes indeed form the [8+2] adduct as a minor product.⁷ Given these considerations, we hypothesized that the first report of a [6+4] cycloaddition could be ambimodal and have a single TS that can lead to both the [6+4] and [8+2] adducts.

Cyclopentadiene and Tropone: Calculated Reaction.

We have calculated the TSs of the reactions of cyclopentadiene with tropone (Figures 2A,B and S2). For the reaction of

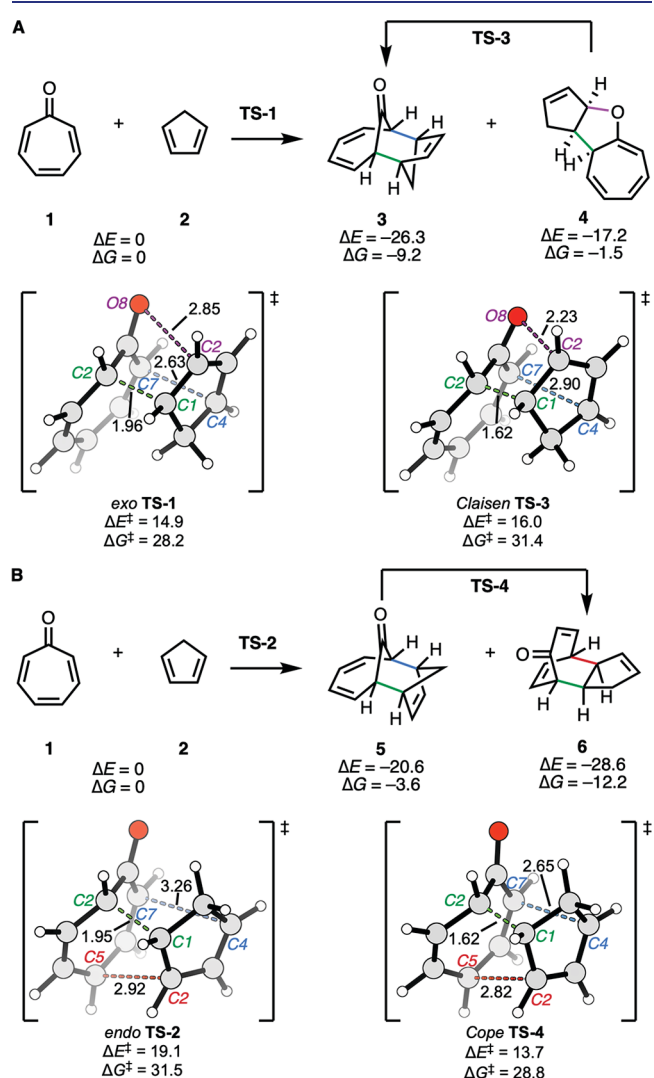


Figure 2. Calculated energy surface for the (A) *exo* (TS-1) and (B) *endo* (TS-2) reactions of tropone (1) and cyclopentadiene (2) at the DLPNO-CCSD(T)/cc-pVQZ// ω B97X-D/def2-TZVP level of theory.

cyclopentadiene and tropone, the *exo* cycloaddition (TS-1) is favored over the *endo* cycloaddition (TS-2) by a difference in Gibbs free energy of activation of 3.3 kcal·mol⁻¹. Using transition-state theory, this energetic difference ($\Delta\Delta G^\ddagger$) corresponds to a predicted product ratio of >99:1 *exo* to *endo*—thus reproducing the experimental result that only the *exo* adduct is observed.

TS-1 and TS-2 feature secondary orbital interactions. In TS-1, the exocyclic oxygen (O8) of tropone forms a stabilizing interaction with the cyclopentadiene C2 (2.85 Å, purple dashed line, Figure 2A). This interaction destroys the bilateral

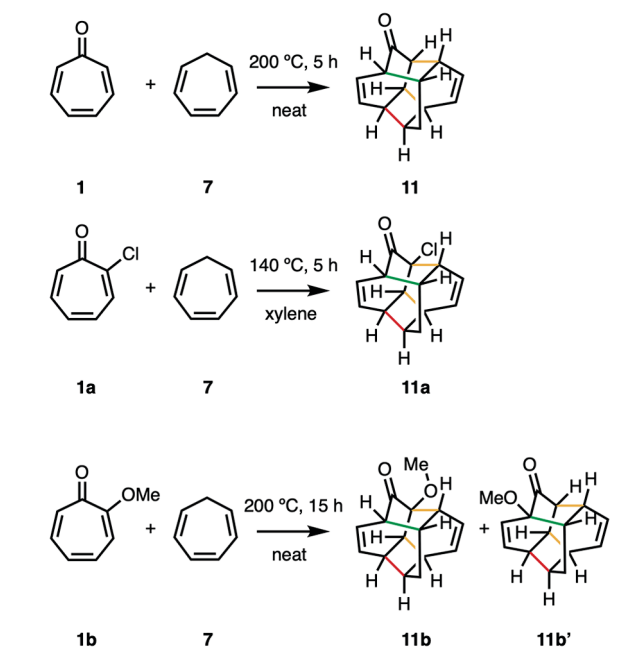
plane of symmetry in TS-1 and makes the *exo*-[6+4] highly asynchronous. By contrast, we previously showed that cyclopentadiene and cycloheptatriene, which lack this secondary interaction, react via a symmetrical and synchronous [6+4] TS.^{34–36} In a typical pericyclic ambimodal TS, the common bond among the reactions is significantly formed at ~ 2 Å, and the competing partial bonds are around ~ 3 Å.³⁷ TS-1 does exhibit ambimodal character, with bond lengths of 1.96, 2.63, and 2.85 Å. However, the orbital overlap between the exocyclic oxygen of tropone and the cyclopentadiene C3 is far from ideal, with an angle of 74° (Supplemental Table S1). The [8+2] product 4 could form, but only as a minor ($\sim 1\%$) product, and it has not been observed in experiments. The higher energy *endo*-TS-2 corroborates the lack of experimental observation of any *endo* products. In this TS, to avoid the unfavorable out-of-phase orbital interaction, cyclopentadiene twists nearly 10° to avoid the unfavorable out-of-phase orbital interaction and to form a favorable orbital interaction between tropone C5 and cyclopentadiene C2. This TS merges the *endo*-[6+4] TS with an *exo*-[4+2] Diels–Alder TS. This twisting makes the *endo*-[6+4] cycloaddition proceed via a single ambimodal *exo*-[4+2]/*endo*-[6+4] TS with forming bonds of 1.95, 2.92, and 3.26 Å. This implies that the *endo*-[6+4] adduct 5 should be a minor product relative to the *exo*-[4+2] adduct 6. Previously, we reported that the competing bond distances in the TS are related to the product ratio, where a difference of 0 Å corresponds to a 50:50 ratio and >0.4 Å corresponds to $<1\%$ of the minor product.³⁷ In TS-2, the difference in bond lengths is 0.3 Å, which correlates to a predicted product ratio of 90:10 6:5.

In ambimodal reactions, the ambimodal TS is connected on the potential energy surface with a second TS that interconverts the products; in these cases, these TSs are Claisen (TS-3) or Cope (TS-4) rearrangement TSs (Figure 2A,B). Typically, in ambimodal cycloadditions, these interconversion TSs are 1 or 2 kcal·mol^{−1} lower in energy than the preceding ambimodal TS.^{25,38} In this case of the *exo* cycloaddition of 1 and 2, the interconversion Claisen TS-3 is higher in energy by 3.2 kcal·mol^{−1}. This indicates that the reverse reaction of 4 is ambimodal and would lead to 1, 2, and 3. This is further evidence that in the forward reaction the [8+2] adduct 4 should not form in an appreciable amount. Further calculations, dynamics, and discussion are in the Supporting Information.

As shown above, the first [6+4] cycloaddition of 1 and 2 is simple experimentally, leading to only a single observable product, but theory reveals the rich complexity of the potential energy surface that lurks behind the scenes, invisible to experiment. The observed product forms via an ambimodal TS that can lead to [6+4] and [8+2] adducts, but forms 3 for dynamic and thermodynamic reasons. The unobserved *endo* TS-2 is similarly ambimodal and complex. These results lead us to hypothesize that all *endo*-[6+4] cycloadditions are ambimodal.

Cycloheptatriene and Tropone: Experiment. About the time of the dawn of pericyclic reactions, the Itô group explored the reactions of the homologous systems, cycloheptatriene and several tropones (Figure 1C, Scheme 1). They found that pentacyclic adducts are formed by [6+4] cycloadditions of the cycloheptatriene as a 6π addend and tropone as a 4π , followed by an intramolecular [4+2] cycloaddition. The reactions of 1 and 2-chlorotropone (1a) with 7 formed a single pentacyclic adduct (11 and 11a), whereas 2-methoxy-

Scheme 1. Itô's Proposed Structures for Products of Cycloaddition Reactions of Tropone Derivatives (1, 1a, 1b) with Cycloheptatriene (7)



tropone (1b) formed a mixture of regioisomers, proposed to be 11b and 11b'.

Cycloheptatriene and Tropone: Frontier Molecular Orbitals. Frontier molecular orbitals indicate that cycloheptatriene 7 should act, like 2, as a nucleophile, with the HOMO at C1 forming a strong interaction at C2 of tropone 1, which is the most electrophilic site of tropone, as indicated by the LUMO coefficient (Figure 1D). This indicates that C6 of 7 interacts with C5 of 1 as well as C4 of 7 with C7 of 1. Arranging 1 and 7 in this geometry allows for two [6+4] cycloadditions to occur, where either molecule can be a 4π or 6π partner. Furthermore, considering the HOMO of 1, we can envision a third, similar interaction as occurs with cyclopentadiene, where C2 of 7 interacts with the exocyclic oxygen (O8) of 1 (Figure S1). In total, frontier molecular orbitals predict that there should be four partially formed bonds in the *exo* TS, and these could, in theory, form two [6+4] adducts and an [8+2] adduct. This means that this reaction could lead to three products from a single tri-pericyclic ambimodal TS, a surmise that we have explored computationally. Because of our long-standing interests to understand periselectivity, we also studied Itô's cycloadditions of the halogenated and methoxylated tropones (Figure 1C, Scheme 1).

Cycloheptatriene and Tropone: Calculated Reaction. The computed potential energy surfaces for the reactions of substituted tropones reacting with cycloheptatriene 7 are shown in Figures 3 and S3. The cycloaddition of 1 and 7 favors the *exo* TS-5 by 2.8 kcal·mol^{−1} (Figure S3). Focusing on TS-5, we note that, as predicted by frontier molecular orbital interactions, there are four partially formed bonds in the TS, with distances of 1.92, 2.84, 3.02, and 3.11 Å. TS-5 has ambimodal character and could lead to three cycloaddition products—two [6+4] adducts and an [8+2] adduct. This would be the second example of a tri-pericyclic reaction.²³ All the potential products have similar energies ($\Delta G = -1.5$ to $+1.0$) when compared to separate reactants, 1 and 7. This

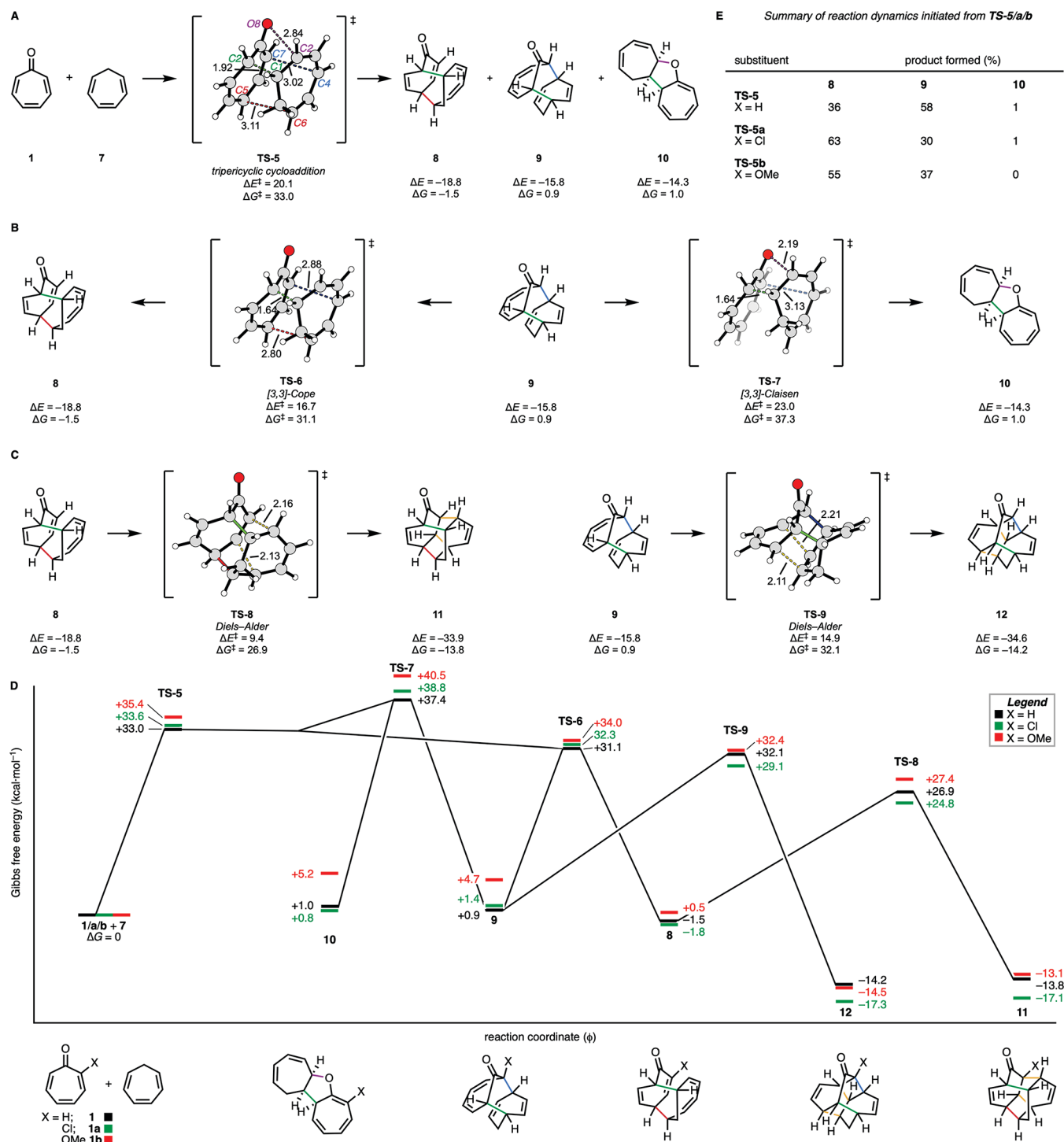


Figure 3. Calculated energy surfaces for tropones reacting with cycloheptatriene (7). (A) Calculated reaction energetics of tropone **1** and cycloheptatriene 7. (B) Interconversion Cope (TS-6) and Claisen (TS-7) pathways of tropone and cycloheptatriene adducts. (C) Diels–Alder TSs (TS-8 and TS-9) leading to pentacyclic adducts. (D) Free energy diagram for tropone (black), chlorotropone (**a**, green), and methoxytropone (**b**, red) reacting with cycloheptatriene. (E) Summary of quasi-classical reaction dynamics trajectory results, indicating ratios of **8**, **9**, and **10** formed from TS-5, TS-5a, and TS-5b. Calculations at the DLPNO-CCSD(T)/cc-pVQZ//ωB97X-D/def2-TZVP level of theory. Dynamics at the optimization level of theory. Energies are quasi-harmonic corrected and reported at 1 M and 25 °C.

indicates that the forward and reverse reactions could occur. Next, we performed an intrinsic reaction coordinate calculation and found that TS-5 leads directly to the [3,3]-sigmatropic Cope rearrangement to TS-6 and then proceeds to product **9** (Figures 3B and S4). TS-6 interconverts the two [6+4] adducts **8** and **9**. We extensively searched for [3,3]- and [5,5]-

sigmatropic Claisen TSs that would interconvert either [6+4] adduct **8** or **9** with the [8+2] adduct **10**. After many efforts, we located the [3,3]-sigmatropic Claisen rearrangement TS-7 that interconverts **10** and **9**. This structure is a very late TS, with the O8–C2 bond distance nearly formed at 2.19 Å, and is very high in energy ($\Delta G^\ddagger = 37.3$), nearly 5 kcal·mol^{−1} higher in

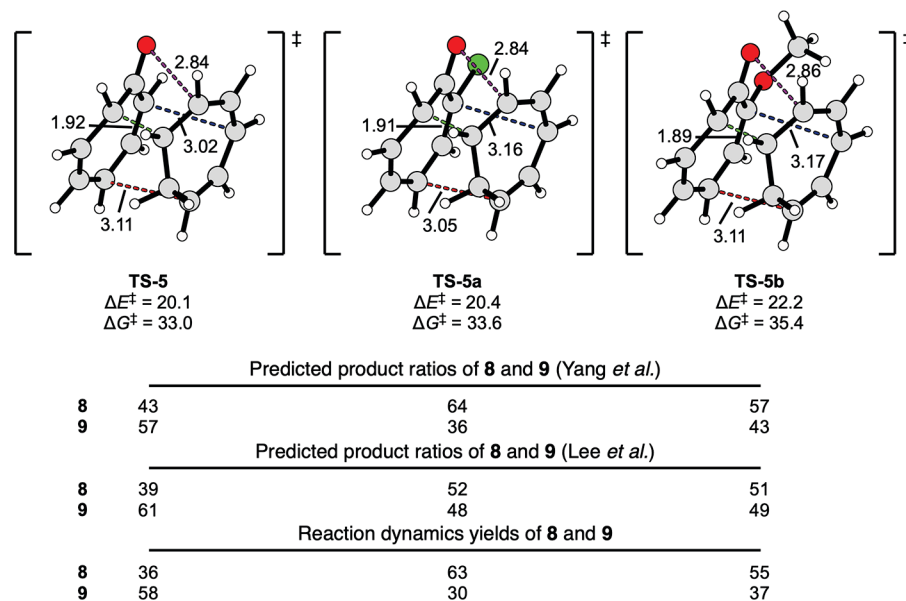


Figure 4. Comparison of tripericyclic TS geometries, energies, and predicted product ratios of **8** and **9** by Yang *et al.*³⁷ and Lee *et al.*⁴⁰ with reaction dynamics yields.

energy than the preceding tripericyclic TS-5. Traversing such a barrier would be an extremely rare event and indicates that a very minor percentage ($\sim 1\%$) of **10** could form momentarily before reverting back to either separated reactants or **9**.

This first cycloaddition step via TS-5 builds a reactive diene in **8** and **9** that is pre-distorted and ready to undergo a subsequent [4+2] Diels–Alder reaction (TS-8 and TS-9). However, **10** does not have such a possibility and is less stable than the reactants, and so it presumably undergoes a retro-[8+2] reaction to re-form **1** and **7**. The barriers for these Diels–Alder TSs, TS-8 and TS-9, are quite different. We hypothesize that this is due to the relative reactivity of the dienophile: the dienophile of **9** is unactivated, whereas the dienophile of **8** is an α,β -unsaturated ketone. We believe that this electronic difference could cause the 5.2 kcal·mol^{−1} difference in $\Delta G^\ddagger$, as the structures are similarly strained with related scaffolds. This electronic difference of the dienophiles in **8** and **9** brings the barrier for TS-8 below that of the interconversion Cope TS-6 and indicates that **9** will convert via TS-6 into **8** and then exclusively form the pentacyclic adduct **11**.

Overall, the calculations predict that this reaction undergoes a tripericyclic cycloaddition (TS-5) to form **8**, **9**, and **10** that then undergo a concomitant Diels–Alder reaction (TS-8 and TS-9) to form the experimentally observed pentacyclic adducts **11** that feature 4-, 5-, 6-, and 7-membered rings. These results reproduce the Itô group's 1967 report. However, our studies indicate that a second adduct, **12**, could form as a minor product. Interestingly, 28 years later, in 1995, Singh published similar findings at a lower temperature (140 °C versus 200 °C).³⁹ In that paper, they reported the sole formation of our predicted minor product **12**. By lowering the temperature, we do not expect the reaction to then “switch” to proceed through the higher-energy TS-9. This reaction warrants further experimental investigation.

We also calculated the chloro- (a) and methoxy- (b) substituted tropones that the Itô group studied, in order to understand how substituents influence the tripericyclic reaction product ratios. We calculated the energy surfaces

with the substituted tropones (Figure 3C). In general, we found that, in the first step, compared to TS-5, the methoxy raises the reaction barriers (TS-5b, +2.4 kcal·mol^{−1}) and the chloro has a small effect on the reaction barriers (TS-5a, +0.6 kcal·mol^{−1}). In the second step, the chloro decreases the Diels–Alder barriers substantially (TS-8a, TS-9a, −2.1 to −3.0 kcal·mol^{−1}) whereas the methoxy has a small effect (TS-8b, TS-9b, +0.3 to +0.5 kcal·mol^{−1}). Of note, the competing Diels–Alder TSs, with either chloro or methoxy substituents, are more facile than the Cope rearrangement TS-6a and TS-6b. This indicates that, in these substituted systems, a second pentacyclic adduct (**12a** and **12b**) should also be observed. Indeed, Itô did observe a second adduct in the reaction of **1b** with **7**. However, this adduct was assigned as the regioisomer **11b'**, while our calculations predict that **12b** should be formed (Figures 3 and S4).

Substitution alters the geometry of TS-5 but does not change the mechanism (Figures 3D and 4). Using the Yang *et al.* bond length model,³⁷ the subtle changes in forming bond lengths in the TS correspond to unique product distributions of **8**, **9**, and **10**. The Yang *et al.* bond length model from our group is a simple method to predict product ratios of ambimodal cycloaddition reactions based on the bond lengths in the TS. Recently, the Goodman group (Lee *et al.*) published a more general method that can be applied to all reaction types.⁴⁰ Upon rounding the predicted ratios, both methods make similar predictions for each reaction (Figure 4). Interestingly, the bond distance between the exocyclic oxygen of **1a/b** and C3 of **7** is the same, and similar to the distance in the aforementioned reaction with **2** (Table S1). We hypothesize that this weak secondary orbital interaction is a geometric requirement due to the proximity to the forming carbon–carbon bonds. Such interactions have been noted in dipolar cycloadditions.^{41,42}

In order to test our predicted product ratios from the tripericyclic transition states TS-5, TS-5a, and TS-5b, we turned to quasi-classical reaction dynamics simulations. The calculations were performed in the gas phase at the ω B97X-D/def2-TZVP level of theory. Trajectories were initiated from

transition-state ensembles generated with ProgDyn and propagated using classical equations of motion with forces calculated quantum mechanically on the fly.^{43,44} Transition-state ensembles were generated by performing a Boltzmann sampling of geometries using normal-mode sampling and adding the zero-point energy for each real normal mode and thermal energy at 298 K to the structures.

Reaction trajectories initiated from TS-5 indicate that the reactants **1** and **7** yield products **8**, **9**, and **10**. This is indeed a tripericyclic reaction, where a single TS leads to three unique products (Figures 3E and 5). Out of 135 trajectories, 46 (36%)

in TS-5b does not alter the product ratio like we saw with a similar distortion in TS-5a. Lastly, the methoxytropone dynamics did not yield **10b**. This is likely due to the small number of trajectories propagated, as the energetics for TS-7a and TS-7b are similarly ~ 5 kcal·mol⁻¹ greater than those for the preceding TS-5a/b.

DISCUSSION

Overall, quantum mechanical calculations revealed the ambimodal nature of the first reported [6+4] cycloaddition of tropone and cyclopentadiene, as well as those more complex examples reported shortly thereafter of substituted tropones and cycloheptatriene. Such results led us to hypothesize on the generality or even requirement for such reactions to be ambimodal.

Here, we postulate that all *endo*-[6+4] cycloadditions are ambimodal. In the interest of clarity, we first define *exo* and *endo* for [6+4] cycloadditions. Previously the definition for Diels–Alder reactions was based upon whether the dienophile substituent is near (proximal, *endo*) or away from (distal, *exo*) the C2 and C3 of the diene, but for [6+4] cycloadditions only the *all-cis* and *s-cis* diene and triene were considered. For [6+4] cycloadditions, several isomers of the triene are possible, and the diene may react from the *s-trans* conformation. Thus, we define *endo* in the [6+4] cycloaddition as the TS or product in which the central unit ($\Delta 3,4$, highlighted) of the triene reaction partner is distal (*exo*) or proximal (*endo*) to the diene reaction partner (Figure 6A). As the triene and diene reaction partners are comprised of smaller π -units, a competing Diels–Alder cycloaddition is always possible. Therefore, in the *endo* orientation, both reactions will occur based solely on spatial orientation. In this case, both reactions share the same favorable frontier molecular orbital interactions. This means that the two reactions will occur through a single ambimodal TS.

Our definitions emphasize the difference between Hoffmann and Woodward's definition of secondary orbital interactions and what we define as subordinate primary interactions (sub-1° in Figure 6B), ~ 3 Å bond lengths in ambimodal TSs. Hoffmann and Woodward defined secondary orbital interactions as those that stabilize or destabilize a TS. This would, for example, be the interaction of C3 of a diene with C3 of a dienophile in a Diels–Alder reaction of two dienes (Figure 6B). Such interactions cannot lead to a stable product. By contrast, subordinate primary interactions lead to a product, as in the interaction of C2 of a diene with C4 of the dienophile (Figure 6B). We propose to call these interactions subordinate primary interactions, as they can compete for bond formation; either subordinate primary interaction can lead to one of the products of the reaction.

To investigate the generality of this concept, we calculated the *endo*-[6+4] TSs for the parent hydrocarbon cyclic and acyclic systems (Figure 6C). These TSs feature strong secondary orbital interactions (subordinate primary interactions) with competing bond lengths of ~ 2.8 and 3.1 Å. In fact, the Diels–Alder is favored in both systems by having a shorter forming bond length in the TS. Earlier in this paper, we described the TSs and orbital interactions for tropones reacting with cyclopentadiene and cycloheptatriene (i.e., TS-1, TS-2, TS-5). In the Itô group's 1970 publication on the cycloadditions of tropone and cyclopentadiene, a minor (4%) *exo*-Diels–Alder adduct was reported, which suggests that our calculated ambimodal *exo*-[4+2]/*endo*-[6+4] TS (TS-2) could

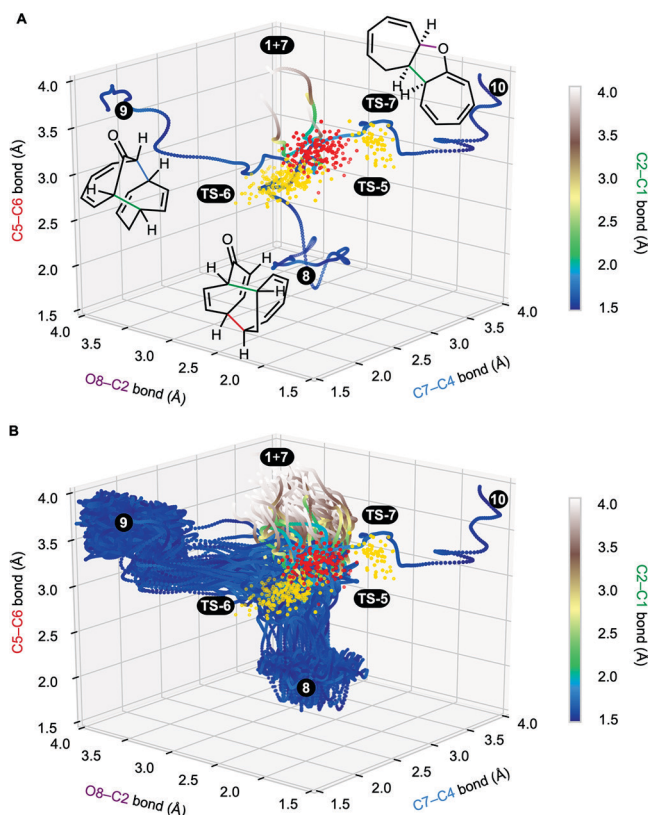


Figure 5. Four-dimensional bond length plots of reaction dynamics trajectories. The color bar maps the common bond (C2–C1, green) among products: separated is gray (4 Å) and formed is blue (1.5 Å). TS ensemble geometries for TS-5 (red), TS-6 (gold), and TS-7 (gold) are overlaid in contrasting colors for clarity. (A) Randomly selected trajectories propagated from TS-5 leading to each product. (B) Plot of all 135 trajectories propagated from TS-5. Calculations are at the ω B97X-D/def2-TZVP level of theory.

form **8**, 82 (58%) form **9**, and 1 (1%) form **10**. The remaining 6 (5%) trajectories recross (defined as traversing the TS region but then recrossing to the product on the other side of the TS).^{36,37} Substitutions of C2 with chloro (a) or methoxy (b) groups alter the product ratios. The 2-chloro substituent inverts the product ratio, where the major product is now **8a** (63%). This can be rationalized by considering the steric effect of substituting the reacting center and can be noted in the TS-5a structure where the forming bond length is stretched out upon chloro substitution when compared to the unsubstituted TS-5 (Figures 3E, 4, and S5). The methoxytropone gives similar product ratios (60% **9**, 40% **8**) to the unsubstituted case, despite having different forming bond lengths in the TS. It is interesting how stretching out the C2–C5 bond by >0.1 Å

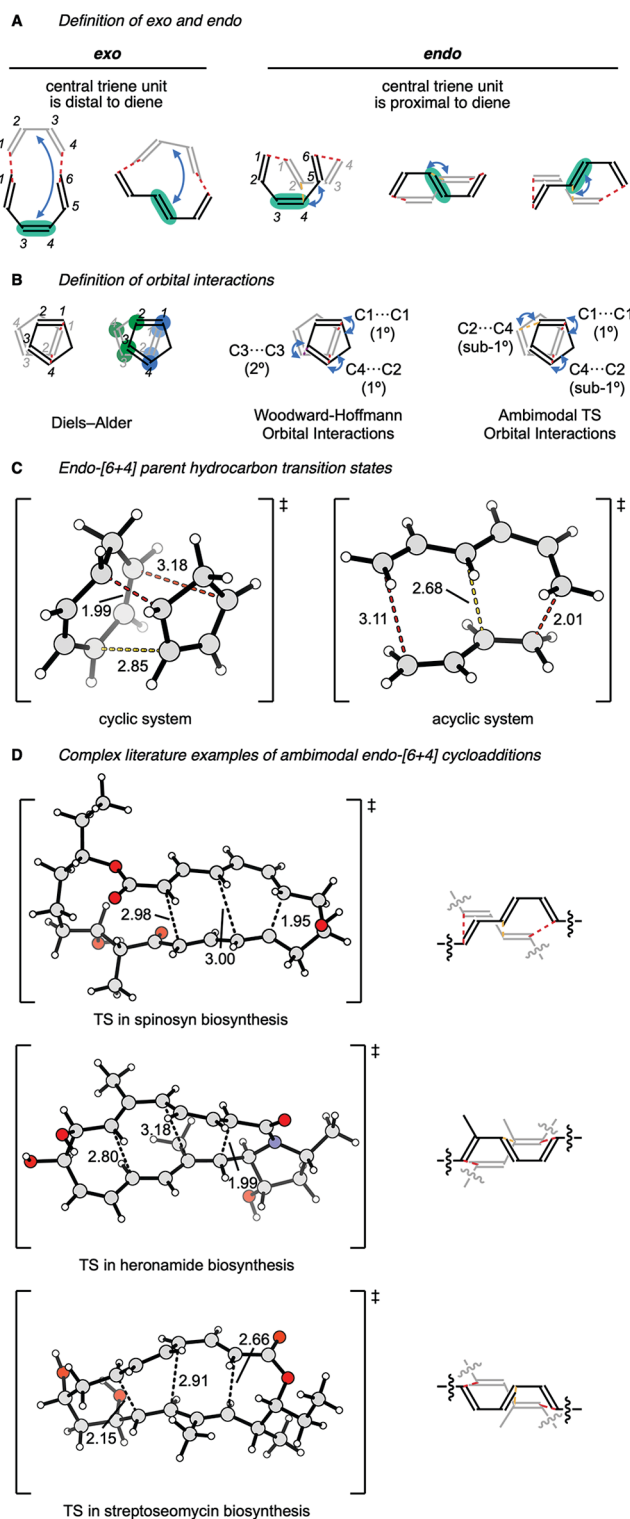


Figure 6. Definitions of (A) *exo* and *endo* with regard to [6+4] cycloadditions, (B) orbital interactions, and (C) parent hydrocarbon transition states of cyclic and acyclic systems. (D) Meta-analysis of complex published examples of *endo*-[6+4] transition states.^{10,11,45}

also be at play.⁶ Those systems agree well with our proposal, but we sought to explore other examples of such *endo*-[6+4] cycloadditions to determine the generality of their ambimodal nature, and three examples are presented in Figure 6D. The examples are calculated TSs in spinosyn, heronamide, and streptoseomycin biosynthesis that feature transannular ambi-

modal cycloadditions.^{10,11,45} Here, we also note that the central triene unit is *endo* with respect to the diene reaction partner in all three examples. These reactions have been characterized in the original publications to be ambimodal. Therefore, all known examples are indeed ambimodal. We conclude, based upon this empirical evidence, that *endo*-[6+4] cycloadditions will always involve ambimodal TSs because of the enforced proximity of atoms that interact and lead to alternative products.

CONCLUSION

We report a computational study that highlights the ambimodal nature of higher-order cycloadditions of tropone (1) with cyclopentadiene (2) and cycloheptatriene (7). The cycloaddition of tropone and cycloheptatriene involves a tripericyclic transition state that leads to the formation of one [8+2] and two [6+4] cycloadducts. The strength of the subordinate primary orbital interactions controls the formation of different cycloadducts. Quasi-classical reaction dynamic simulations resulted in three different products, with one of the [6+4] adducts as the major product, in accordance with the TS geometry. Such simulations revealed the dynamic nature of secondary orbital interactions morphing into primary bond-forming interactions. We have clarified this situation by defining subordinate primary interactions that may or may not lead to a product, depending on the trajectory. In the reactions of cycloheptatriene with various tropones, subsequent intramolecular [4+2] Diels–Alder reactions form the experimentally observed pentacyclic adducts 11 and 12. All of these results point to the overarching concept that all *endo*-[6+4] reactions are ambimodal. To verify our hypothesis, we analyzed the parent hydrocarbon systems, the reactions of 1, 2, and 7, and the known complex examples found in biosynthesis. This empirical evidence confirms our postulate that all *endo*-[6+4] reactions are ambimodal.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.0c13401>.

Computational methodologies, additional calculations, and Cartesian coordinates of calculated structures, including Supplemental Tables S1 and S2 and Figures S1–S5 (PDF)

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

DFT, density functional theory; DLPNO-CCSD(T), domain-based local pair natural orbital coupled cluster theory with single, double, and perturbative triple excitations; HOMO, highest occupied molecular orbital; LUMO, lowest unoccupied molecular orbital; TS, transition state

REFERENCES

- (1) Hoffmann, R.; Woodward, R. B. Selection Rules for Concerted Cycloaddition Reactions. *J. Am. Chem. Soc.* **1965**, *87* (9), 2046–2048.
- (2) Woodward, R. B.; Hoffmann, R. The Conservation of Orbital Symmetry. *Angew. Chem., Int. Ed. Engl.* **1969**, *8* (11), 781–853.
- (3) Hoffmann, R.; Woodward, R. B. Orbital Symmetries and Endo-Exo Relationships in Concerted Cycloaddition Reactions. *J. Am. Chem. Soc.* **1965**, *87* (19), 4388–4389.
- (4) Cookson, R. C.; Drake, B. V.; Hudec, J.; Morrison, A. The Adduct of Tropone and Cyclopentadiene: A New Type of Cyclic Reaction. *Chem. Commun.* **1966**, No. 1, 15–16.
- (5) Itô, S.; Fujise, Y.; Okuda, T.; Inoue, Y. Reaction of Tropone with Cyclopentadiene. *Bull. Chem. Soc. Jpn.* **1966**, *39* (6), 1351.
- (6) Itô, S.; Sakan, K.; Fujise, Y. Cycloaddition Reaction of Tropone and Cyclopentadiene. *Tetrahedron Lett.* **1970**, *11* (33), 2873–2876.
- (7) Houk, K. N.; Woodward, R. B. Cycloaddition Reactions of Tropone and 2,5-Dimethyl-3,4-Diphenylcyclopentadienone. *J. Am. Chem. Soc.* **1970**, *92* (13), 4145–4147.
- (8) Mcleod, D.; Thøgersen, M. K.; Jessen, N. I.; Jørgensen, K. A.; Jamieson, C. S.; Xue, X. S.; Houk, K. N.; Liu, F.; Hoffmann, R. Expanding the Frontiers of Higher-Order Cycloadditions. *Acc. Chem. Res.* **2019**, *52* (12), 3488–3501.
- (9) Jamieson, C. S.; Ohashi, M.; Liu, F.; Tang, Y.; Houk, K. N. The Expanding World of Biosynthetic Pericyclases: Cooperation of Experiment and Theory for Discovery. *Nat. Prod. Rep.* **2019**, *36* (5), 698–713.
- (10) Zhang, B.; Wang, K. B.; Wang, W.; Wang, X.; Liu, F.; Zhu, J.; Shi, J.; Li, L. Y.; Han, H.; Xu, K.; et al. Enzyme-Catalysed [6+4] Cycloadditions in the Biosynthesis of Natural Products. *Nature* **2019**, *568* (7750), 122–126.
- (11) Patel, A.; Chen, Z.; Yang, Z.; Gutiérrez, O.; Liu, H.; Houk, K. N.; Singleton, D. A. Dynamically Complex [6+4] and [4+2] Cycloadditions in the Biosynthesis of Spinosyn A. *J. Am. Chem. Soc.* **2016**, *138* (11), 3631–3634.
- (12) Kim, H. J.; Ruzsyczky, M. W.; Choi, S.; Liu, Y.; Liu, H. Enzyme-Catalysed [4+2] Cycloaddition Is a Key Step in the Biosynthesis of Spinosyn A. *Nature* **2011**, *473*, 109.
- (13) Itô, S.; Fujise, Y.; Woods, M. C. Pentacyclo-[7.5.0.02,7.05,13.06,12]Tetradeca-3,10-Dien-8-One. *Tetrahedron Lett.* **1967**, *8* (12), 1059–1064.
- (14) Itô, S.; Fujise, Y.; Sato, M. Structure Determination of 2-Methoxytropone-Cycloheptatriene Adducts by Mass Spectrometry. *Tetrahedron Lett.* **1969**, *10* (9), 691–694.
- (15) Fukazawa, Y.; Ito, S.; Iitaka, Y. The Crystal and Molecular Structure of 2-Chlorotropone-Cycloheptatriene Adduct. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1969**, *25* (4), 665–673.
- (16) Fujise, Y.; Nakatsu, T.; Itô, S. Acetolysis of Pentacyclo-[7.5.0.02,7.05,13.06,12]Tetradeca-3, 10-Dien-8-Yl Toluene-p-Sulfonate. *Tetrahedron Lett.* **1975**, *16* (44), 3821–3824.
- (17) Caramella, P.; Quadrelli, P.; Toma, L. An Unexpected Bispericyclic Transition Structure Leading to 4+2 and 2+4 Cycloadducts in the Endo Dimerization of Cyclopentadiene. *J. Am. Chem. Soc.* **2002**, *124* (7), 1130–1131.
- (18) Pham, H. V.; Houk, K. N. Diels–Alder Reactions of Allene with Benzene and Butadiene: Concerted, Stepwise, and Ambimodal Transition States. *J. Org. Chem.* **2014**, *79* (19), 8968–8976.
- (19) Hare, S. R.; Tantillo, D. J. Post-Transition State Bifurcations Gain Momentum – Current State of the Field. *Pure Appl. Chem.* **2017**, *89* (6), 679–698.
- (20) Caramella, P.; Quadrelli, P.; Toma, L.; Romano, S.; Khuong, K. S.; Northrop, B.; Houk, K. N. The Three Corrugated Surfaces of 1,4-Divinyltetramethylene Diradical Intermediates and Their Connections to 1,2-Divinylocyclobutane, 4-Vinylcyclohexene, 1,5-Cyclooctadiene, and Two Butadienes. *J. Org. Chem.* **2005**, *70* (8), 2994–3008.
- (21) Wang, Z.; Hirschi, J. S.; Singleton, D. A. Recrossing and Dynamic Matching Effects on Selectivity in a Diels–Alder Reaction. *Angew. Chem., Int. Ed.* **2009**, *48* (48), 9156–9159.
- (22) Gonzalez-James, O. M.; Kwan, E. E.; Singleton, D. A. Entropic Intermediates and Hidden Rate-Limiting Steps in Seemingly Concerted Cycloadditions. Observation, Prediction, and Origin of an Isotope Effect on Recrossing. *J. Am. Chem. Soc.* **2012**, *134* (4), 1914–1917.
- (23) Hong, Y. J.; Tantillo, D. J. Biosynthetic Consequences of Multiple Sequential Post-Transition-State Bifurcations. *Nat. Chem.* **2014**, *6* (2), 104–111.
- (24) Ess, D. H.; Wheeler, S. E.; Iafe, R. G.; Xu, L.; Çelebi-Ölçüm, N.; Houk, K. N. Bifurcations on Potential Energy Surfaces of Organic Reactions. *Angew. Chem., Int. Ed.* **2008**, *47* (40), 7592–7601.
- (25) Xue, X. S.; Jamieson, C. S.; Garcia-Borràs, M.; Dong, X.; Yang, Z.; Houk, K. N. Ambimodal Trispericyclic Transition State and Dynamic Control of Periselectivity. *J. Am. Chem. Soc.* **2019**, *141* (3), 1217–1221.
- (26) Guo, Y.; Riplinger, C.; Becker, U.; Liakos, D. G.; Minenkov, Y.; Cavallo, L.; Neese, F. Communication: An Improved Linear Scaling Perturbative Triples Correction for the Domain Based Local Pair-Natural Orbital Based Singles and Doubles Coupled Cluster Method [DLPNO-CCSD(T)]. *J. Chem. Phys.* **2018**, *148* (1), 011101.
- (27) Dunning, T. H. Gaussian Basis Sets for Use in Correlated Molecular Calculations. I. The Atoms Boron through Neon and Hydrogen. *J. Chem. Phys.* **1989**, *90* (2), 1007–1023.
- (28) Chai, J.-D.; Head-Gordon, M. Long-Range Corrected Hybrid Density Functionals with Damped Atom–Atom Dispersion Corrections. *Phys. Chem. Chem. Phys.* **2008**, *10* (44), 6615–6620.
- (29) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. A Consistent and Accurate Ab Initio Parametrization of Density Functional Dispersion Correction (DFT-D) for the 94 Elements H–Pu. *J. Chem. Phys.* **2010**, *132* (15), 154104.
- (30) Weigend, F.; Ahlrichs, R. Balanced Basis Sets of Split Valence, Triple Zeta Valence and Quadruple Zeta Valence Quality for H to Rn: Design and Assessment of Accuracy. *Phys. Chem. Chem. Phys.* **2005**, *7* (18), 3297–3305.
- (31) Neese, F. The ORCA Program System. *Wiley Interdiscip. Rev.: Comput. Mol. Sci.* **2012**, *2* (1), 73–78.
- (32) Neese, F. Software Update: The ORCA Program System, Version 4.0. *Wiley Interdiscip. Rev.: Comput. Mol. Sci.* **2018**, *8* (1), No. e1327.
- (33) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; et al. *Gaussian 16*, Revision A.03; Gaussian Inc., 2016.

- (34) Goldstein, E.; Beno, B. R.; Houk, K. N. Transition Structures and Exo/Endo Stereoselectivities of Concerted [6+4] Cycloadditions with Density Functional Theory. *Theor. Chem. Acc.* **1999**, *103* (1), 81–84.
- (35) Houk, K. N.; Gonzalez, J.; Li, Y. Pericyclic Reaction Transition States: Passions and Punctilios, 1935–1995. *Acc. Chem. Res.* **1995**, *28* (2), 81–90.
- (36) Leach, A. G.; Goldstein, E.; Houk, K. N. A Cornucopia of Cycloadducts: Theoretical Predictions of the Mechanisms and Products of the Reactions of Cyclopentadiene with Cycloheptatriene. *J. Am. Chem. Soc.* **2003**, *125* (27), 8330–8339.
- (37) Yang, Z.; Dong, X.; Yu, Y.; Yu, P.; Li, Y.; Jamieson, C.; Houk, K. N. N. Relationships between Product Ratios in Ambimodal Pericyclic Reactions and Bond Lengths in Transition Structures. *J. Am. Chem. Soc.* **2018**, *140* (8), 3061–3067.
- (38) Yu, P.; Chen, T. Q.; Yang, Z.; He, C. Q.; Patel, A.; Lam, Y.; Liu, C.-Y.; Houk, K. N. Mechanisms and Origins of Periselectivity of the Ambimodal { $6+4$ } Cycloadditions of Tropone to Dimethylfulvene. *J. Am. Chem. Soc.* **2017**, *139* (24), 8251–8258.
- (39) Singh, V. Periselective Reactions of Tropone: A Novel Tandem $\Pi_6s+\Pi_4s$, $\Pi_4s+\Pi_2s$ Reaction with Cycloheptatriene and $\Pi_4s+\Pi_2s$ Cycloaddition with Cyclohexa-2,4-Dienone. *Indian J. Chem. Sect. B* **1995**, *34B* (10), 847–850.
- (40) Lee, S.; Goodman, J. M. Rapid Route-Finding for Bifurcating Organic Reactions. *J. Am. Chem. Soc.* **2020**, *142* (20), 9210–9219.
- (41) Burns, J. M. Computational Evidence for a Reaction Pathway Bifurcation in Sasaki-Type (4+3)-Cycloadditions. *Org. Biomol. Chem.* **2018**, *16* (11), 1828–1836.
- (42) Chen, S.; Yu, P.; Houk, K. N. Ambimodal Dipolar/Diels–Alder Cycloaddition Transition States Involving Proton Transfers. *J. Am. Chem. Soc.* **2018**, *140* (51), 18124–18131.
- (43) Singleton, D. A.; Hang, C.; Szymanski, M. J.; Greenwald, E. E. A New Form of Kinetic Isotope Effect. Dynamic Effects on Isotopic Selectivity and Regioselectivity. *J. Am. Chem. Soc.* **2003**, *125* (5), 1176–1177.
- (44) Bailey, J. O.; Singleton, D. A. Failure and Redemption of Statistical and Nonstatistical Rate Theories in the Hydroboration of Alkenes. *J. Am. Chem. Soc.* **2017**, *139* (44), 15710–15723.
- (45) Yu, P.; Patel, A.; Houk, K. N. Transannular [6+4] and Ambimodal Cycloaddition in the Biosynthesis of Heronamide A. *J. Am. Chem. Soc.* **2015**, *137* (42), 13518–13523.