# 'Concerted' Transition State, Stepwise Mechanism. Dynamics Effects in C2-C6 Enyne Allene Cyclizations

Tefsit Bekele[‡], **Chad F. Christian**[†], **Mark A. Lipton**[‡], and **Daniel A. Singleton**[†]

‡*Department of Chemistry, Purdue University, West Lafayette, Indiana 47907*

†*Department of Chemistry, Texas A&M University, PO Box 30012, College Station, Texas 77842*

Abstract

The C^2-C^6 (Schmittel)/ene cyclization of enyne-allenes is studied by a combination of kinetic isotope effects, theoretical calculations, and dynamics trajectories. For the cyclization of allenol acetate **9**, the isotope effect (k_{CH3}/k_{CD3}) is approximately 1.43. The isotope effect is interpreted in terms of a highly asynchronous transition state near the concerted/stepwise boundary. This is supported by density functional theory calculations that locate a highly asynchronous transition structure for the concerted ene reaction. However, calculations of both the experimental system and a model reaction were unable to locate a transition structure for formation of the diradical intermediate of a stepwise mechanism. The stepwise mechanism and the asynchronous concerted mechanism start out geometrically similar, and the two pathways appear to have merged as far as the initial transition structure. For the model reaction, quasiclassical direct dynamics trajectories emanating from the initial transition structure afforded the diradical intermediate in 29 out of 101 trajectories. A large portion of the remaining trajectories complete hydrogen transfer before carbon-carbon bond formation, despite the advanced carbon-carbon bond formation in the asynchronous transition structure. Overall, the single minimum-energy path from starting material to product is inadequate to describe the reaction, and a consideration of dynamic effects is necessary to understand the mechanism. The implications of these observations toward questions of concert in other reactions is discussed.

The formation of reactive diradical intermediates in the thermal cyclizations of enediynes and enyne-allenes is both fundamentally intriguing and biologically momentous.[1,2] Myers[3] and Saito[4] showed that enyne-allenes (**1**) undergo thermal C^2-C^7 cyclizations to afford α,3-tolyl diradicals (**2**), and this is thought to be the key step in the biological activation of neocarzinostatin A.[2b] The ability of simple reactants to form such highly reactive intermediates is usually attributed to the aromaticity gained on cyclization. Schmittel, however, established a second reaction motif for enyne-allenes in which C^2-C^6 cyclization affords products apparently derived from fulvenyl diradicals (**3**).[5,6,7] This cyclization gains no aromaticity but is still promoted by the formation of a strong sp^2–sp^2 sigma bond from sp-hybridized carbons. The Schmittel cyclization motif has proven valuable in synthesis and has received extensive interest.[8]
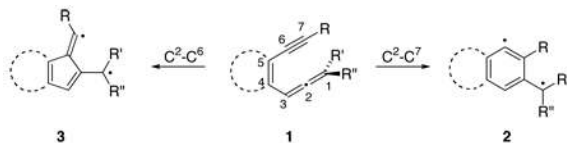
Evidence for the intermediacy of a diradical in the C^2-C^6 cyclization of enyne-allenes has included trapping with 1,4-cyclohexadiene[7] (Scheme 1) as well as the observation of double stranded DNA cleavage by structures known to undergo the Schmittel-type cyclization. Schmittel found that changing solvent polarity did not affect the rate of reaction or product ratios, leading him to rule out zwitterionic intermediates.

Theoretical studies on the cyclization of the parent (Z)-1,2,4-heptatrien-6-yne have supported a diradical mechanism for the C^2-C^6 cyclization.[9] In this system the C^2-C^7 cyclization is predicted to be favored over C^2-C^6 by approximately 10 kcal/mol, consistent with the experimental observation of exclusive C^2-C^7 cyclization.[10] The C^2-C^6 cyclization is predicted to be relatively favored by benzannulation,[11] and it is also favored by bulky terminal substituents and radical stabilizing groups at C^7. Studies in one of our laboratories have demonstrated an interesting acceleration of the C^2-C^6 cyclization by oxyanion substituents.[12]

When the enyne-allene is substituted by an alkyl group at C^1, the ultimate product of the C^2-C^6 cyclization has undergone hydrogen transfer from the alkyl substituent to C^7 and the overall conversion is formally an ene reaction (Scheme 2). The ene reaction is allowed as a concerted pericyclic process, but as a whole, ene reactions have been notably mechanistically diverse. Concerted mechanisms have been experimentally supported often,[13,14] yet many ene reactions have been found to involve more complex mechanisms.[14,15,16] The mechanism of any given ene reaction may be considered uncertain in the absence of evidence, but the mechanistic ambiguity of these reactions of enyne-allenes seems particularly interesting. In this case, the two-step mechanism involving a diradical intermediate is imminently credible based on the chemistry in Scheme 1. In a theoretical study by Engels, the two-step and concerted mechanisms were predicted to have nearly equal free energies of activation.[17] Engels suggested that the two mechanisms could be distinguished using kinetic isotope effects, as have been applied to many ene reactions.

The energetic similarity of concerted and two-step mechanisms in these reactions raises fundamental issues. By the Thornton hypothesis,[18] when the intermediate for a potential two-step mechanism is low in energy, the transition state for the corresponding concerted process should geometrically approach the stepwise process. As the intermediate goes lower in energy, the concerted mechanism ultimately transitions into the stepwise pathway. However, the nature of mechanisms at the concerted / stepwise boundary is not well understood. Should such reactions involve a mixture of mechanisms?[19] What is the effect of intrinsic entropic differences between a two-step mechanism and a more organized concerted process?

We describe here a combined experimental and theoretical study of the C^2-C^6 / ene cyclization of enyne-allenes, a reaction with a mechanism at the concerted / stepwise boundary. We find that this reaction is not well-described by either concerted or two-step labels, and that the consideration of dynamic effects is necessary to understand the nature of these intriguing reactions.

Results

Kinetic Isotope Effect

The allenol acetate **9** was chosen for study owing to its clean conversion to the cyclized product **10** at a moderate temperature and rate. Both the unlabeled substrate **9a** and the deuterium labeled **9b** were prepared by the addition of the appropriate Gilman reagent to the acetylenic ketone **8** by a previously reported procedure.[12] The deuterium incorporation in **9b** prepared in this way is >98% based on ^{1}H NMR analysis.
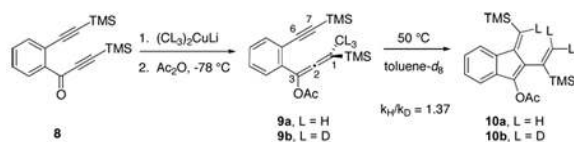
The cyclization of **8** in toluene-d_8 at 50 °C was conveniently followed by ^{1}H NMR. The conversion of **9a** versus time was consistent with a first-order process over the course of the reaction with a half-life of ≈9000 s, and first-order kinetics were assumed in rate-constant determinations. The conversion of **9** to **10** was monitored by the intensity of characteristic aromatic signals for each relative to the residual methyl signal of toluene-d_8 used as an internal standard. The signals corresponding to the acetate and TMS groups were unsuitable due to peak overlap. ^{1}H NMR spectra were collected at 30-minute intervals until no further change in relative peak heights was observable, and the resulting data were fit directly as a first-order process (see Supporting Information). The isotope effect for the reaction was determined from both the disappearance of **9** and appearance of **10** in two reactions each for labeled and unlabeled materials, affording a total of four measurements with an average k_{CH3}/k_{CD3} of 1.43 and a standard deviation of 0.12. This standard deviation may underestimate the uncertainty in k_H/k_D because only two completely independent reactions are involved.

This isotope effect will be discussed in more detail below, but we note here that the k_H/k_D is smaller than normally observed in concerted ene reactions.[13d,14a,15g,20] However, the k_H/k_D is qualitatively too large to support a stepwise ene process. This is in line with the idea that the mechanism is near the concerted / stepwise boundary.

Theoretical Pathways from 9

Engels has previously reported extensive careful calculations on the C^2-C^6 cyclization of a series of enyne-allenes capable of undergoing the overall ene conversion.[17] The focus here is in two areas – the reaction of the experimental system **9** and a more detailed study of a model system. The results of these studies suggested a more complex picture of the reaction mechanism than would conventionally be considered.

Three possible pathways for the C^2-C^6 cyclization of **9** were explored in restricted and unrestricted B3LYP calculations employing a 6–31G(d,p) basis set (Figure 1). The first is direct formation of **10** by a concerted process. Transition structure **11**[‡] was located for this conversion, and the predicted barrier of 23.8 kcal/mol is well consistent with a reaction that proceeds in a few hours at 50 °C. (The predicted half-life at 50 °C after inclusion of an entropy estimate based on the unscaled harmonic frequencies is a fortuitous 8900 s.) The second possible pathway is cyclization of **9** with an "inward" rotation of the methyl group on C^1 to afford diradical **12**. Intramolecular hydrogen transfer in **12** could then afford product **10** via transition structure **13**[‡]. As will be considered in greater detail below, no transition structure could be located for the formation of **12** from **9**. The third possible pathway is cyclization of **9** with an "outward" rotation of the methyl group on C^1 to afford diradical **15** via transition structure **14**[‡]. This cyclization has the effect of running together the two trimethylsilyl groups and is rather sterically encumbered. As a result, the predicted barrier for this cyclization is 8.8 kcal/mol above that for the ene pathway. Based on this result and the absence of experimental support for long-lived diradicals in this reaction,[12] this pathway is unlikely to be experimentally relevant.

It should be noted that the predicted energies of **12** and **15** are dubious due to spin contamination ($<S^2>$ is 0.43, 0.09, 0.04, and 0.47 for **12**, **13**[‡], **14**[‡], and **15**, respectively). The diradical energies will be considered further for a model reaction. Structure **11**[‡] was identical for restricted and unrestricted calculations and its wavefunction was spin-unrestricted stable.

All attempts to locate a transition structure for formation of **12** failed, using both restricted and unrestricted calculations. Instead, the saddle-point searches invariably converged on **11**. This is in agreement with the observations of Musch and Engels, who reported for a similar cyclization that a transition structure for formation of a diradical could not be located when the C^7 methyl group twists toward the alkyne.[17] An attempt to locate a transition structure for formation of **12** in UBPW91/6-31G(d,p) calculations also converged instead on a transition structure similar to **11**‡ (See the Supporting Information.)

How could there be no transition structure for formation of **12**? Both **11**‡ and a hypothetical transition structure for formation of **12** would involve formation of the C^2-C^6 bond, and the difference between the two is that **11**‡ also involves hydrogen transfer. However, the degree to which hydrogen transfer has progressed in **11**‡ is very minor – the breaking C–H bond is only slightly elongated compared to **9**. As a result, the structure of **11**‡ is very close to that expected for a transition structure forming **12**. Rather than involving two separate transition structures with extremely similar geometries, it appears that the stepwise and concerted pathways have merged in the single transition structure **11**‡. The significance of this observation will be explored in more detail after the interpretation of the experimental kinetic isotope effect is considered.

Predicted Isotope Effects

To aid in interpreting the experimental H/D isotope effect, predicted isotope effects based on transition structures **11**‡ and **14**‡ were calculated. These predictions used the scaled theoretical vibrational frequencies[21] in conventional transition state theory by the method of Bigeleisen and Mayer.[22] For the secondary H/D isotope effect associated with transition structure **14**‡, a tunneling correction was applied using a one-dimensional infinite parabolic barrier model.[23] No tunneling correction was applied for the prediction of the primary H/D isotope effect associated with transition structure **11**‡, and the resulting prediction is likely a lower bound compared to a complete treatment of tunneling and variational transition state effects (impractical in this case).

The idea behind the prediction of an isotope effect for transition structure **14**‡ is that **14**‡ may serve as a surrogate for a transition structure that would lead to diradical **12**. The predicted k_{CH3}/k_{CD3} at 50 °C for **14**‡ is 1.06. This is slightly greater than unity because the adjacent radical character in **14**‡ has the effect of weakening the C-H bonds in the methyl group on C^1, but this prediction is much smaller than the experimental isotope effect. This appears to exclude rate-limiting formation of the diradical, but for reasons that will soon be clear, we opt for a more careful wording: the experimental isotope effect is inconsistent with a predominant rate-limiting transition state involving C^2-C^6 ring closure without partial C–H bond breakage.

The predicted k_{CH3}/k_{CD3} based on **11**‡ is 1.54. Qualitatively, both this predicted isotope effect and the experimental isotope effect of ≈1.43 are in the realm of very small primary isotope effects. The difference is perhaps small enough to ignore – the experimental isotope effect is consistent with the qualitative nature of **11**‡ in which C–H bond breakage has progressed to a minimal extent. However, it is enlightening for the discussion later to consider possible origins for the difference between the experimental and predicted isotope effects. Aside from experimental error, the simplest explanation is inaccuracy in **11**‡. In this regard, the smaller observed isotope effect suggests that the progress of C–H bond breaking in the experimental transition state is less than in **11**‡. An alternative, more complex, explanation is that the observed isotope effect represents a mixture of concerted and two-step mechanisms. These two possibilities are distinct in classical physical organic terms, but the difference will be less well defined when dynamics are considered below.

Theoretical Pathways in a Model Reaction

In order to explore the C^2-C^6 / ene cyclization in more detail and with higher-level calculations, the model cyclization of **16** was studied. Stationary-point geometries for the reaction path were optimized in restricted or unrestricted B3LYP calculations employing a 6-311+G(d,p) basis set. Single-point energies were then computed using Brueckner orbitals including double excitations and a perturbative estimate of triple excitations (BD(T)),[24] employing a 6-31+G (d,p) basis set. An unrestricted wavefunction was employed for diradical structures; for other structures the difference between unrestricted and restricted BD(T) results was negligible. The applicability and accuracy of this calculational approach was supported by studies of the thermodynamics of cyclizations of *cis*-hex-3-en-1,5-diyne to *p*-benzyne (eq 1) and hepta-1,2,4-trien-6-yne to α,3-didehydrotoluene (eq 2), which can be compared with reported experimental data.[25,26] In both cases, the predicted cyclization energies [(U)BD(T)//6-31+G(d,p)//(U) B3LYP/6-311+G(d,p) + thermal correction for 25 °C] are within the uncertainty of the experimental values.
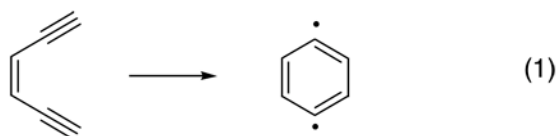
ΔH_{expt} = 8.5 ± 1.0 kcal/mol (ref 25)
ΔH_{calcd} = 8.5 kcal/mol
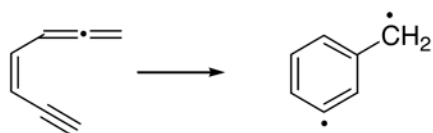
ΔH_{expt} = -15 ± 4 kcal/mol (ref 26)
ΔH_{calcd} = -11.6 kcal/mol

The results for the cyclization of **16** are summarized in Figure 2. Transition structure **17**‡ was located for the concerted formation of product **18** from **16**. This structure is similar to **11**‡, with substantial C^2-C^6 bond formation but little progress in the hydrogen transfer from the methyl group on C^1 to C^7. As was the case for **9**, no transition structure could be located for formation of diradical **19** from **16**. Our search for such a transition structure included imposing constraints to preclude hydrogen transfer in the transition structure. Invariably, when the constraints were removed, the transition structure converged to **17**‡. An attempt to locate a transition structure for formation of **19** in MP2/6-31G(d,p) calculations also converged instead on a transition structure similar to **17**‡ (See the Supporting Information.) Two transition structures for the formation of *E-Z* isomers of **19** were located, and these are shown in Supporting Information. Since our focus is on the energy surface in the area of **17**‡, **19**, and **20**‡ as a model for the experimental reaction of **9** and the energy surface in the area of **11**‡, **12**, and **13**‡, we did not explore the likely-favored C^2-C^7 cyclization of **16**.

Figure 2 also shows how the BD(T)/6-31+G(d,p)//(U)B3LYP/6-311+G(d,p) energies compare with those obtained for **16**–**20** in (U)B3LYP/6-31G(d,p) calculations (the calculations used for **9**–**15**, and for dynamics below). The DFT approach performs well in predicting the reaction barrier, as previously suggested by the comparison with experiment, but slightly overestimates the stability of diradical **19**. This is unsurprising as **19** is subject to spin contamination (($<S^2>$ = 0.28). The barrier for product formation from **19** is estimated reasonably. Overall, the DFT calculations appear to reproduce the key features of the energy surface.

Dynamics

The fascinating common feature in the C^2-C^6 cyclization of **9** and the model **16** is the absence of a separate transition state for formation of diradicals **12** and **19**. This observation is reminiscent of recent discussions in the literature, by one of us and by others, of reactions in which a single initial transition state can lead to two separate products.[16,27,28,29] We hypothesized that the energy surface in these cyclizations has the qualitative features shown in Figure 3. From the rate-limiting transition structures **11‡** or **17‡**, the steepest-descent path in mass-weighted coordinates (the "minimum energy path") affords the ene product. A standard theoretical analysis would thus conclude that the ene reaction occurs in a concerted fashion. However, continued formation of the new C^2-C^6 bond from **11‡** or **17‡** without concomitant hydrogen transfer could lead in a downhill process to **12** or **19**. It was thus possible that trajectories passing through the "concerted" ene transition state could lead to the diradical intermediate. In such a situation, whether a significant proportion of the reaction involves a stepwise process, and the competition between concerted and stepwise mechanisms, becomes a question of dynamics.

To study this issue, **17‡** was used as the starting point for quasiclassical direct dynamics trajectories on the UB3LYP/6-31G(d,p) surface. With all atomic motions freely variable, the trajectories were initialized by giving each vibrational mode a random sign for its initial velocity, along with an initial energy based on a random Boltzmann sampling of vibrational levels appropriate for 323.15 K, including zero point energy. The mode associated with the imaginary frequency was treated as a translation and given a Boltzmann sampling of translational energy "forward" over the col. Two processes were explored for assigning the starting atomic positions. In the first, the geometry of **17‡** was used as the starting point, forcing all trajectories to go through **17‡** exactly. In the second, the starting atomic positions on the potential energy ridge in the area of **17‡** were randomized using a linear sampling of possible harmonic classical displacements for each normal mode, adjusting the kinetic energy for each mode accordingly. The two processes ultimately gave similar results. Forces were calculated directly at the UB3LYP/6-31G(d,p) level at each point, and employing a Verlet algorithm, 1-fs steps were taken until either the ene product **18** was formed (defined by a C^2-C^6 distance < 1.5 Å with a C^7-H distance < 1.1 Å) or diradical **19** was formed (defined by a C^2-C^6 distance < 1.5 Å with the C^7-H distance increased to > 2.1 Å). The median time for product formation was 30 fs, and all trajectories were complete within 85 fs. With such short simulation times, the effect of intramolecular vibrational energy redistribution[30] should be minimal. A graph of C^2-C^6 versus C^7-H distances for some typical dynamics trajectories is shown in Figure 4.

The results were striking. Although the minimum energy path from **17‡** smoothly affords **18**, 29 out of 101 trajectories afforded diradical **19**. Five of the 29 trajectories entering the area of **19** were followed for an additional 100 fs, but none of these went on to **18**. It thus appears that *an intermediate is formed in a substantial portion of trajectories proceeding via the transition structure for the concerted ene reaction*. These intermediate diradicals would ultimately go on to **18**, but since the barrier (via **20‡**) is substantial, the time scale for the simulation is insufficient to observe this transformation.

A second remarkable observation was that many trajectories underwent rapid hydrogen transfer to C^7 without simultaneous C^2-C^6 bond formation. Out of 101 trajectories, 29 saw the C^7-H distance decrease to < 1.1 Å while the C^2-C^6 distance was still > 1.8 Å. Seven trajectories had the C^7-H distance decrease to < 1.1 Å while the C^2-C^6 distance increased to > 2.0 Å. Such trajectories pass through a geometry resembling structure **21**. No potential-energy minimum associated with this structure could be located, and all of the trajectories go on rapidly to **18**. The intervention of structures resembling **21** thus has no outward consequence. Nonetheless, the surprising prevalence of trajectories through the area of **21** would seem to impact the conception of asynchronicity in pericyclic reactions. Structure **17‡** would be described as

highly asynchronous, with the C^2-C^6 bond formation preceding hydrogen transition, but despite this, *many trajectories complete the hydrogen transfer first.*


21
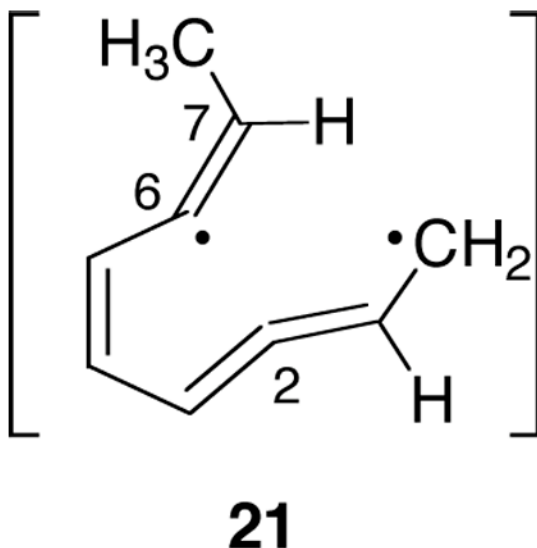
Discussion

Within conventional physical organic chemistry, much has been made of the distinction between concerted and stepwise mechanisms for reactions with multiple bonding changes. This is seemingly a well-defined problem – concerted mechanisms occur by a pathway involving a single transition state and no intermediate, while a stepwise mechanism passes through at least two transition states with an intervening intermediate. The steps of a stepwise mechanism are always conceivably kinetically distinguishable, that is, separately influenceable. A concerted mechanism, in contrast, has a single kinetic barrier, and any factor that influences product formation or selectivity must equivalently influence starting material disappearance. A sufficiently detailed characterization of a reaction's transition state, whether it be experimental (substituent effects, isotope effects, entropy of activation, volume of activation, spectroscopic observation, etc.) or theoretical, is considered adequate to distinguish between stepwise and concerted mechanisms, at least in principle. The possibility that a mixture of separate stepwise and concerted mechanisms can be operative is well recognized, but this adds no essential complication. The borderline between stepwise and concerted mechanisms is classically straightforward – does the mechanistic pathway involve an intermediate, or does it not?

Dynamic effects complicate the situation. Carpenter and others have discussed extensively the situation in which dynamic trajectories pass through the area of an intermediate without equilibration of vibrational energy.[31,32,33] As a result, the product selectivity doesn't reflect the presence of an intermediate or the presence of a second kinetically distinguishable step. In effect, the mechanistic pathway follows the energy surface of a stepwise mechanism but the reaction "acts" concerted in observables, for example in stereochemistry.

Recent work by Yamataka, Aida, and Dupuis has further complicated the distinction between stepwise and concerted mechanisms.[34] In theoretical calculations on the ionization of **22**, the minimum-energy path on the potential energy surface passes through transition structure **23** to afford the tertiary cation **24**. In this conversion, loss of the water leaving group and methyl-group rearrangement occur in a concerted fashion. However, dynamics simulations found that most trajectories at 400 K afforded initially the secondary cation **25**. This cation is not

"connected" to the starting material by a minimum-energy path, but can be formed readily by a process that simply breaks the C—O bond without concurrent methyl rearrangement. In effect, the reaction proceeds by a stepwise process while a classical analysis would predict a concerted process. A thermodynamic interpretation of this observation is that, in contrast to the potential energy surface, the canonical variational transition state on the free-energy surface leads to the secondary cation.
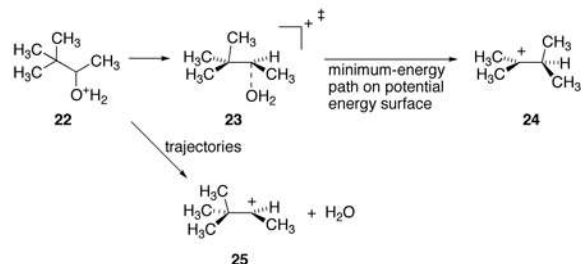
The results here suggest a new wrinkle on the impact of dynamics on the idea of stepwise versus concerted mechanisms, a wrinkle that is potentially widespread. The observed kinetic isotope effect and the calculational results both support the idea that the C^2-C^6/ene cyclization of **9** is near the stepwise/concerted boundary. It might be envisioned that in such cases, separate stepwise and concerted mechanisms could be competitive. Here, such a competition cannot be ruled out from the experimental isotope effect alone, but the calculations support a merging of the stepwise and concerted pathways as far as the rate-limiting transition state. Under these circumstances, experimental mechanistic probes of this transition state would appear to implicate an exclusively concerted reaction. Going on from this transition state, however, an intermediate may or may not be formed, depending on the dynamics of individual trajectories. The intermediate could in principle be trapped or detected, implicating the stepwise mechanism. Kinetic observations and trapping experiments would appear contradictory.

It is enlightening to qualitatively consider the ene reactions of **9** or **16** within the context of a More O'Ferrall-Jencks diagram (Figure 5).[35] Ene reaction mechanisms can be very complicated, but here we restrict our consideration to having carbon-carbon bond formation and hydrogen transfer as the dominant dimensions for the More O'Ferrall-Jencks diagram. [13a] Because the overall reaction is exothermic, it would be expected that the transition state would be relatively early, and since the diradical intermediate after carbon-carbon bond formation is relatively stable (as evidenced by the chemistry of Scheme I), the transition state should be shifted toward the edge of the diagram, as shown. This is consistent with the predicted transition structures **11**[‡] and **17**[‡], as well as the experimental isotope effect with **9**. The normal qualitative understanding of these reactions would then be based on a smooth reaction path passing through the transition state. However, a broad range of structures are energetically downhill from the transition state, and it is possible for trajectories to depart drastically from the qualitative reaction path. This can include reaching an intermediate in the corner of the More O'Ferrall-Jencks diagram that is not on the reaction path.

The concept of a reaction path between starting material and product is fundamental in the chemistry paradigm. In the absence of bifurcations, such paths can be mathematically well-defined, the common definition as the steepest-descent path in mass-weighted coordinates being only one example out of many possibilities. It is of course well understood that real trajectories do not follow exactly the reaction path. However, qualitative discussions of reaction mechanisms implicitly assume the existence of a path that is chemically representative of the ensemble of trajectories connecting starting material and product. The technical justification for this view is that trajectories should tend to regress toward a minimum-energy path. However, such regression will not necessarily overcome the thermal divergence of trajectories,

outside of the bottleneck area of a transition state. When trajectories vary sufficiently, no single reaction path can adequately describe the mechanism. This appears to be the case for the current reaction.

It is fascinating to consider the possible applicability of the ideas here in other pericyclic reactions. Many cycloadditions, for example, have been predicted to occur by concerted processes through highly asynchronous transition states. In many such cases, both the cycloaddition product and the intermediate for a stepwise cycloaddition may be downhill from the rate-limiting transition state.[36] If so, trajectories passing through the "concerted transition state" could conceivably lead to intermediates in substantial amounts. A theoretical study that merely characterized the stationary points and minimum-energy paths in a mechanism could not resolve whether intermediates were formed, no matter how accurate the calculation. Notably, kinetic mechanistic probes of such reactions would be completely incapable of deciding whether intermediates were formed. Stereochemical and trapping probes could still be applied, though the conventional limitations of such probes have been discussed extensively[37] and, as described above, dynamic effects can make stepwise mechanisms appear stereochemically concerted.[31,32a–c,38] It should be of considerable interest to explore the degree to which such dynamic effects complicate diverse pericyclic mechanisms.

Conclusions

The KIE (k_{CH3}/k_{CD3}) for the C^2-C^6 / ene cyclization of **9** is approximately 1.43. This appears qualitatively too large to be a secondary isotope effect for formation of a diradical, and the theoretically predicted KIE based on diradical-forming **14**[‡] supports this conclusion. The 1.43 value is very small for a primary H/D KIE, but it appears roughly consistent with the predicted isotope effect of 1.54 based on **11**[‡]. From the observed isotope effect alone, we cannot rule out a mixture of standard concerted and two-step mechanisms. However, the theoretical calculations do not support a conventional mixture of mechanisms, and the simplest interpretation of the isotope effect is that the ene reaction involves a highly asynchronous transition state, near the concerted / stepwise boundary, in which hydrogen transfer has progressed to a minimal extent.

No transition structure could be located for formation of diradical **12** from **9** or diradical **19** from **16**. The initial geometry changes associated with these stepwise processes would be expected to be very similar to those for the highly asynchronous concerted mechanism, and the stepwise and concerted pathways have apparently merged as far as the rate-limiting transition structures. From these structures, the minimum-energy path leads to the ene product, but it is also downhill to the diradical intermediates.

Quasiclassical direct dynamics trajectories emanating from **17**[‡] vary greatly. Although **17**[‡] would normally be considered the transition state for a concerted reaction, many trajectories lead to an intermediate. A large alternative portion of the trajectories complete hydrogen transfer before full carbon-carbon bond formation, in contrast to what would be expected from the asynchronicity of the transition structure. The *single* minimum-energy path from starting material to product does not adequately describe the mechanism.

The ideas of transition state theory and reaction paths are so entwined in the mechanistic understanding of chemistry that they limit the questions that may be asked regarding a mechanism and the answers that may arise from mechanistic studies. When a reaction involves multiple bonding changes, a standard question has been whether the bonding changes occur by a stepwise or concerted pathway. When the question is asked this way, the only possible answers are that the reaction proceeds by a concerted pathway, or by a stepwise pathway, or by a mixture of the two separate pathways. Advances in the understanding of dynamic effects

in mechanisms[16,27,31,32,33,34] have shown that the question of concerted versus stepwise is too simple, and that the answer to the question may be very complicated indeed. The consideration of a possible role for dynamic effects, even for complex reactions in solution, should be incorporated into the mechanistic chemistry paradigm.

Experimental Section

Kinetic studies

The unlabelled allenol acetate **9a**[12] (10 mg, 0.028 mmol) was dissolved in toluene-d_8(0.075 mL) and transferred to an NMR tube and immediately placed into the probe of a Varian Inova 300 MHz NMR spectrometer to minimize spontaneous cyclization of **9a**. Prior to the experiment, the variable temperature thermostat of the NMR was calibrated using an ethylene glycol standard by measuring its chemical shift at 50 °C. The heights of selected aromatic protons of **9a** and the cyclization product **10a** were monitored by ^{1}H NMR at 50 °C over 6 h until no further change in the heights of the aromatic protons was observed. Data were collected every 30 min and normalized to the height of the residual methyl signal of toluene-d_8. The same procedure was carried out for the deuterated allenol acetate **9b**, and both experiments were repeated. In each case no side products were observable and the formation of product appeared essentially quantitative. Kinetic isotope effect values were computed by plotting the selected ^{1}H-NMR peak heights against time and fitting the data to a first-order simulation to obtain rate constants for the cyclization of both **9a** and **9b**. The two replications were used to obtain averaged values and standard deviations for the observed kinetic isotope effects.

Supplementary Material

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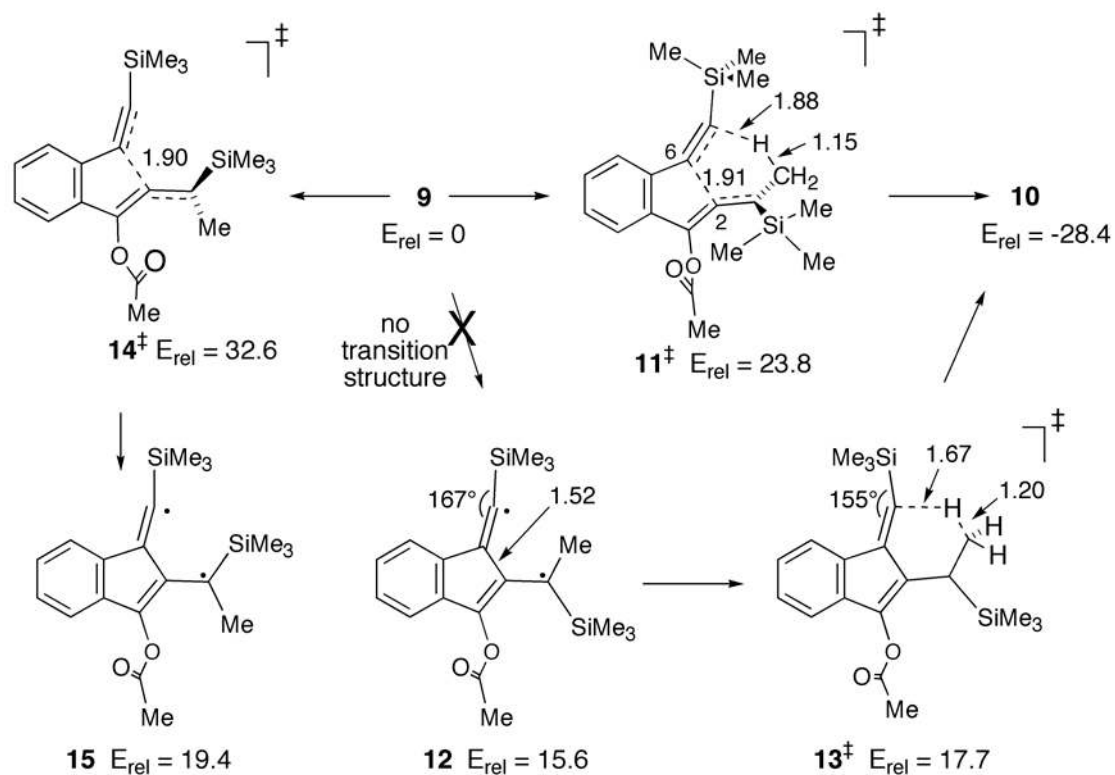
Figure 1.
Predicted pathways for the cyclization of **9** in (U)B3LYP/6-31G(d,p) calculations. Structures **12**, **13**‡, **14**‡, and **15** were obtained using unrestricted calculations, while the remaining structures were identical in restricted and unrestricted calculations. Relative energies are in kcal/mol and include zpe.
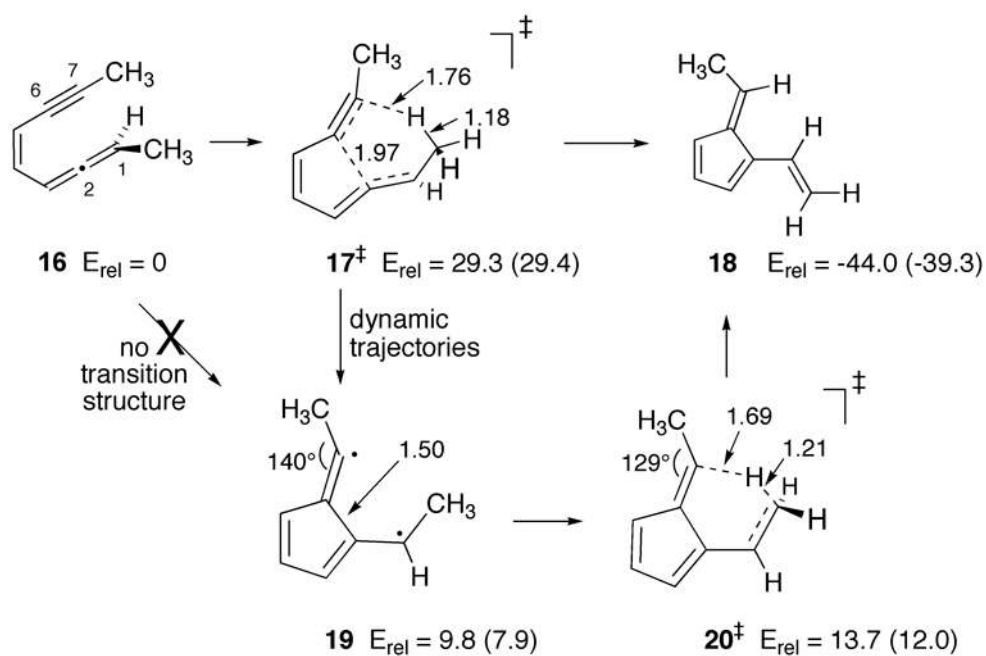
Figure 2.
Predicted pathways for the cyclization of **16**. Structures **19** and **20**‡ were obtained using unrestricted calculations. The relative energies (kcal/mol) shown are (U)BD(T)/6-31+G(d,p)// B3LYP/6-311+G(d,p) + zpe. Relative (U)B3LYP/6-31G(d,p) energies are shown in parentheses for comparison.
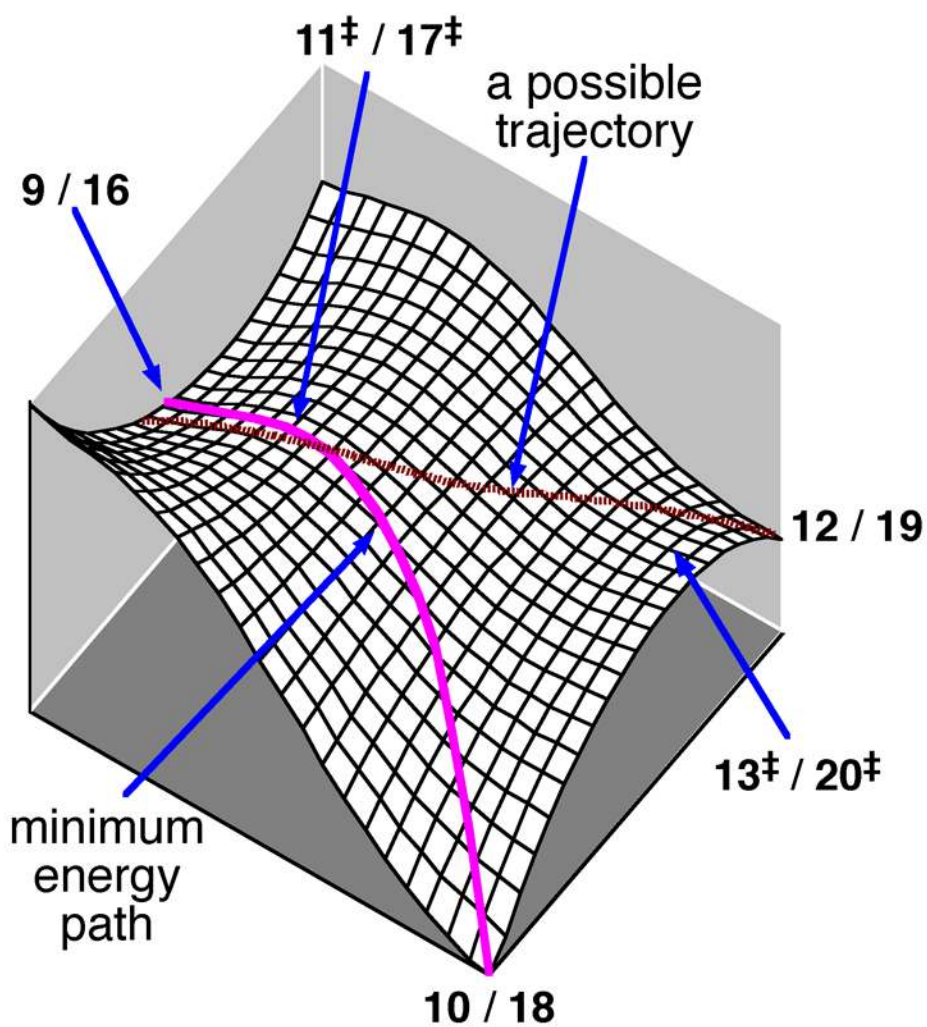
Figure 3.
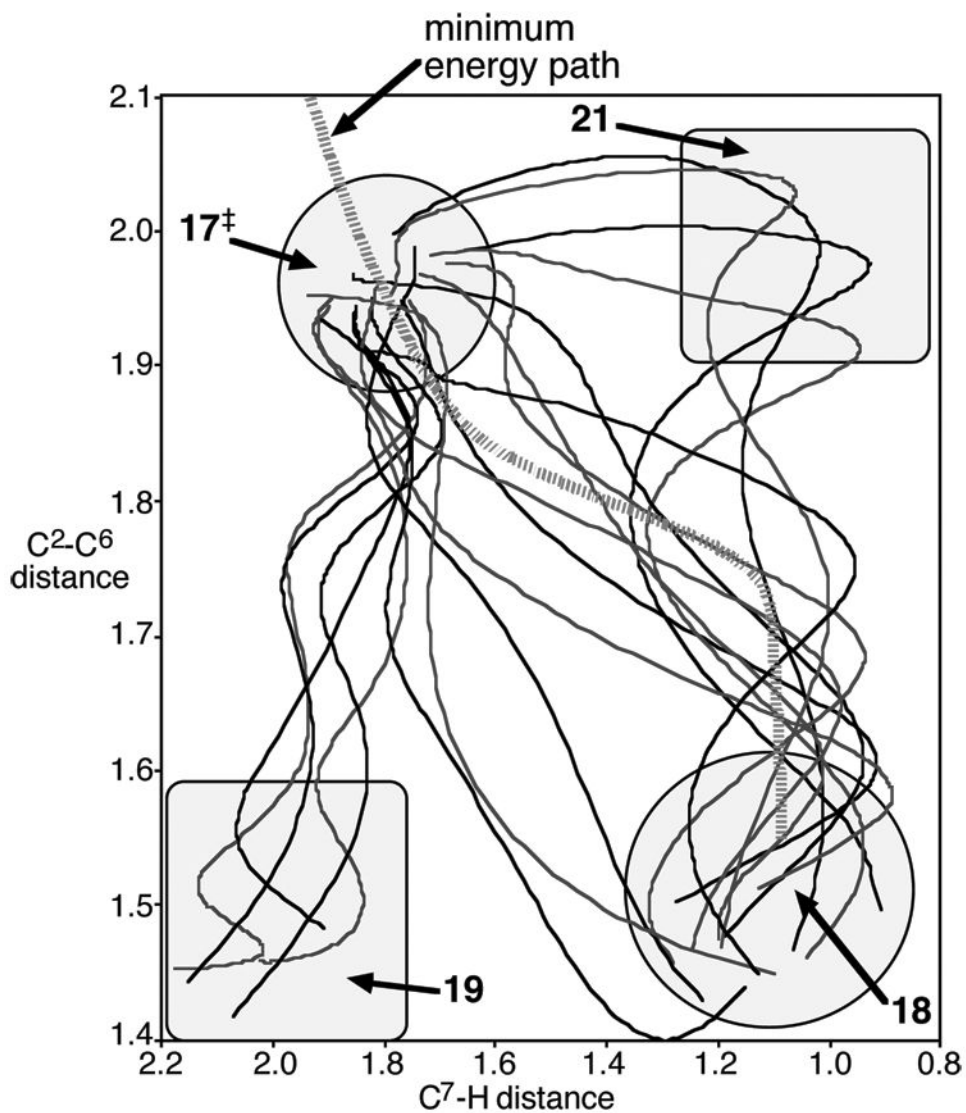Qualitative energy surface for the cyclizations of **9** and **16**.

Figure 4.
Graph of C^2-C^6 versus C^7-H distances for selected dynamics trajectories starting from **17‡**, along with the steepest-descent pathway through **17** is mass-weighted coordinates (the minimum energy path).
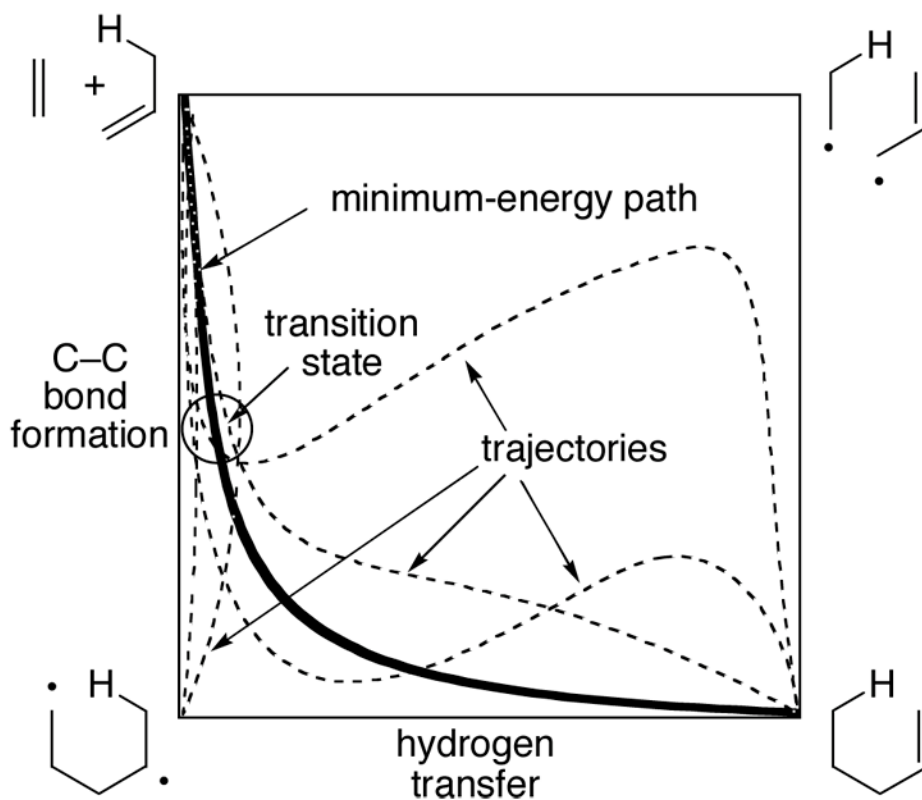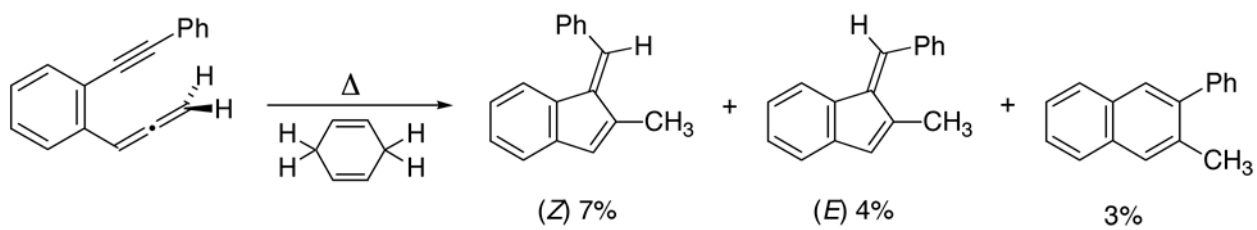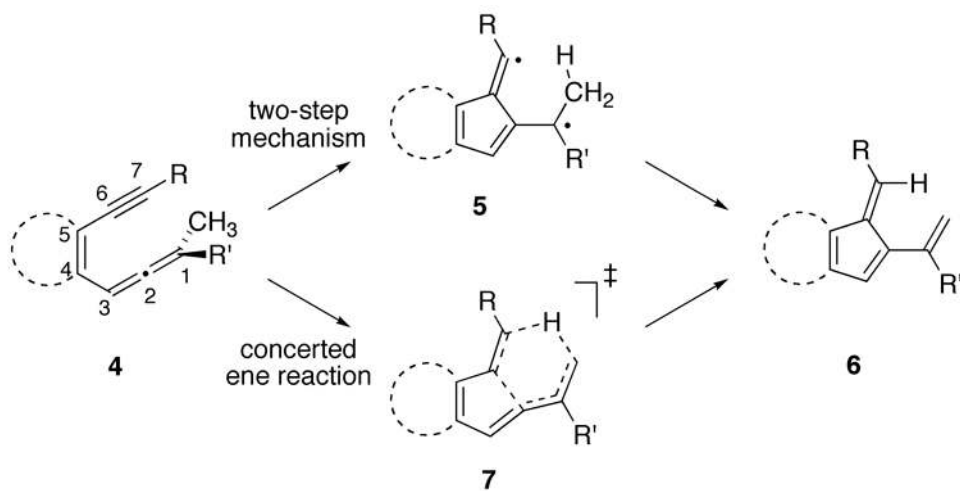
Figure 5.
More O'Ferrall-Jencks diagram for ene reactions. The approximate minimum-energy path expected for reaction of **9** or **16** is shown as a solid bold line. Possible qualitative trajectories are shown as dotted lines.

Scheme 1.

Scheme 2.