

Elucidation of Nonstatistical Dynamic Effects in the Cyclization of Enyne Allenes by Means of Kinetic Isotope Effects**

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In the first decades following the birth of physical organic chemistry, a set of firm paradigms guided our conception of reactive intermediates, transition states, and reaction coordinates. More recently, the significance of dynamic effects in organic reactions has become increasingly evident through the seminal work conducted by Carpenter,^[1] Singleton,^[2] Doubleday,^[3] Hase,^[4] and others.^[5] It was suggested quite often in the context of unimolecular reactions proceeding at the boundary between concerted versus stepwise mechanisms that dynamic effects cause a behavior differing from that predicted by statistical kinetic models, such as the transition-state theory.^[1,4]

Additional reaction mechanisms at the concerted/stepwise boundary^[1,4,6] with strongly contributing dynamic effects have been recently resolved.^[1,2a,5c,7] However, experimental substantiation of nonstatistical dynamic effects, mostly based on kinetic isotope effects (KIE) or stereochemical information, was usually limited to single case studies and thus needed to be complemented by computational dynamic simulations. Herein, we describe how dynamic effects become manifest in experimental inter- and intramolecular KIE^[8] data at the concerted/stepwise boundary of the thermal C²–C⁶ cyclization of enyne allenes **E** (Scheme 1).^[9,10] For compounds **E** with a wide range of substituents, the KIE

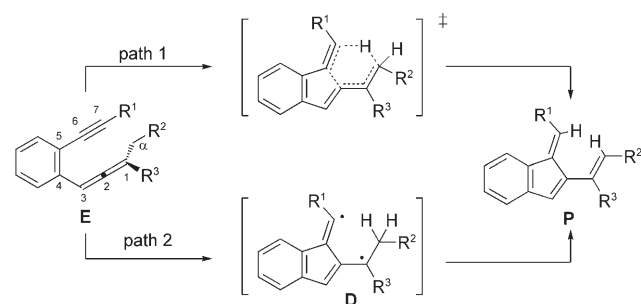
results defy the primacy of statistical kinetic models. Thus our data will serve as a copious test case for the validation of future dynamic trajectory computations.

A few years ago, Engels and co-workers investigated the ene reaction of enyne allenes at the (U)B3LYP/6-31G(d) level. They predicted a stepwise process with the radical-stabilizing group R¹ = Ph and a concerted process with R¹ = *t*Bu.^[11] A recent study of the intermolecular KIE on the thermal ene process of enyne allene **E4** with R¹ = triisopropylsilyl (TIPS), however, suggested a stepwise diradical process.^[10] Lipton and Singleton analyzed the reaction for **E1** by combining insight from a single intermolecular KIE value, theoretical calculations, and dynamic trajectories.^[12] The intermolecular KIE^{exp} = 1.43 concurred persuasively with the theoretically predicted value for a concerted ene process (KIE^{calcd} = 1.54). They suggested, based on computations and a relatively small number of thermalized trajectories, that both stepwise and concerted ene reactions of enyne allenes proceed via a single transition state (TS) and that dynamic effects at a posttransition-state valley–ridge inflection point determine which pathway is taken. While this was clearly a fascinating proposal, the Lipton/Singleton proposal has not found clear experimental support to date.

To sort out the different views arising from the above experimental work we decided to prepare a set of [D₀]-, [D₁]-, and [D₂]enyne allenes and to investigate their inter- and intramolecular KIEs in the thermal ene reaction (Table 1). Classical statistical kinetic models would predict that inter- and intramolecular KIEs for a concerted process are close to each other, differing only in contributions from secondary effects, while for a stepwise process the isotopic patterns need not correspond. For the latter case, the intermolecular KIE should be roughly 1.00–1.05^[8c-e,g,j] and the intramolecular KIE significantly higher than unity.

We chose the benzannulated enyne allenes **E2**–**E5** containing bulky groups such as TIPS, trimethylsilyl (TMS), and *t*Bu, at the alkyne terminus, as well as TMS and aryl groups at the allene terminus. Our intent with the aryl group was to test the effect of a radical-stabilizing group on the diradical to favor the stepwise over the concerted process.

Compounds **E4** and **E5** exhibit intermolecular KIEs of 1.17 and 1.08, respectively, which are close to unity but not within the range expected from statistical kinetic models.^[8c-e,g,j] To understand the meaning of these values, we also measured intramolecular KIEs. Neither the values for [D₁]**E4** and [D₁]**E5** (1.003 and 1.001) nor their temperature independence (see Table 2, [D₁]**E5**), however, can be understood in classical terms. It is clear, though, that both intra- and intermolecular KIEs rigorously refute a purely concerted mechanism and point rather to a stepwise process (Scheme 1,



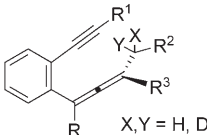
Scheme 1. The thermal C²–C⁶ cyclization of enyne allenes: concerted (path 1) and stepwise (path 2) reaction mechanisms.

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Table 1: Intermolecular and intramolecular kinetic isotope effects for the ene reaction of enyne allenes **E1–E5**.

Cmpd.		Intermol. KIE (D_0/D_2)	Intramol. KIE (D_1)	Prevailing character of the mechanism
E1	R = OAc, R^1 = TMS, R^2 = H, R^3 = TMS	1.43 ^[a]	—	concerted
E2	R = H, R^1 = TMS, R^2 = n Pr, R^3 = TMS	1.60 ^[b]	1.352 ^[b]	concerted
E3	R = H, R^1 = t Bu, R^2 = n Pr, R^3 = TMS	1.24 ^[c]	1.286 ^[c]	boundary
E4	R = H, R^1 = TIPS, R^2 = n Pr, R^3 = p -An	1.17 ^{[d], [e]}	1.003 ^[d]	stepwise
E5	R = H, R^1 = TMS, R^2 = n Pr, R^3 = p -An	1.08 ^[f]	1.001 ^[f]	stepwise

[a] Ref. [12]. [b] At 90 °C. [c] At 125 °C. [d] At 100 °C. [e] Ref. [10]. [f] At 80 °C.

Table 2: Temperature dependence of intramolecular kinetic isotope effects for the ene reaction of **E2** and **E5**.

T [°C]	Intramol. KIE [D_1] E2	Intramol. KIE [D_1] E5
60	1.706	1.003
70	1.561	1.002
80	1.486	1.001
90	1.352	1.001
110	1.075	1.002

path 2). This interpretation is fully consistent with the recently observed cyclopropyl ring-opening in the thermolysis of **E4'** (cf. **E4** with R^2 = 2,2-diphenylcyclopropyl instead of n Pr).^[13] Rewardingly, the Lipton/Singleton model^[12] provides a thorough explanation for the experimental KIEs. Accordingly, the intermolecular KIEs of 1.08 and 1.17 propose that the prevailing stepwise trajectories mix with a small amount of concerted trajectories (going directly to **P**), thus raising the KIE above 1.05. If one assumes that the main fraction proceeds via the diradical, the near-unity intramolecular KIE implies that the hydrogen transfer itself is again controlled by a nonstatistical dynamic process. Apparently the diradical is formed in a very shallow energy minimum with large excess energy preventing statistical kinetic behavior.^[14]

While **E4** and **E5** are characterized by aryl substituents at the allene terminus which provide momentum towards stepwise diradical formation, **E1–E3** are devoid of radical-stabilizing substituents. As evident in Table 1, an intermolecular KIE of 1.60 was derived from the thermolysis of [D_0, D_2]**E2**, comparable to that of allenyl acetate **E1**.^[12] The intramolecular KIE for [D_1]**E2** was measured to 1.352 and proved to be temperature-dependent (Table 2). Remarkably, both the inter- and intramolecular KIEs are decisively different from unity and deviate more from each other than can possibly be due to secondary isotopic effects.^[15] While these KIEs are more consistent with a concerted mechanism (Scheme 1, path 1), they are rather low compared to those of prototypical ene reactions.^[8a, b] As in classical terms, inter- and intramolecular KIEs should match closely for a concerted mechanism, the experimental discrepancy seems to reflect, as suggested by the Lipton/Singleton model,^[12] the mixing of concerted and stepwise trajectories, with the former ones clearly dominating.

For **E3**, intra- and intermolecular KIEs lie between those of **E1, E2** and **E4, E5**. **E3** seems to be located in the boundary zone of the concerted-to-stepwise thermal ene reaction of enyne allenes as it shows an intermolecular KIE close to that of **E4, E5** but an intramolecular KIE close to that of **E2**. Remarkably, the intramolecular KIE is larger than the intermolecular. Although the full meaning of the KIE data of **E3** has to be inquired further, the intermolecular KIE data suggests a balanced mixing of concerted and stepwise trajectories. In order to account for the KIEs in **E3** (intramolecular > intermolecular), the intramolecular KIE of the “pristine stepwise” trajectories must be higher than those measured for **E4, E5**. This may be a result of a sterically imposed barrier for the hydrogen transfer from **D** → **P** as a result of the large *tert*-butyl group at the alkyne terminus.

In order to sharpen the mechanistic picture in light of the variety of KIEs displayed by **E1–E5** we reinvestigated the potential energy surface of the thermal ene process of **E6** (R^1 = CH₃, R^2 = R^3 = H, no benzannulation). Owing to the absence of any radical-stabilizing group, **E6** should represent a prototypical enyne allene following the “concerted” mechanism. While a single transition state was located for the concerted and stepwise process in an earlier computation,^[12] our fully optimized (U)B3LYP/6-31G(d) 2D energy surface of the C²–C⁶ cyclization displays a broad transition-state zone about TS1. At TS1 we find the following results: $\Delta E^\ddagger$ (+ZPE) = 31.2 (29.7), $\Delta\Delta H_{298}^\ddagger$ = 28.7, $\Delta\Delta G_{298}^\ddagger$ = 32.2; k_{CH_3}/k_{CD_3} = 1.61, k_{CH_3}/k_{CH_2D} = 1.57; C_α –H = 115.5 pm, C²–C⁶ = 195.7 pm; barrier heights in kcal mol^{–1}).^[3c, 16] As shown in Figure 1—where energies are given relative to diradical **D**—there is a smooth increase in energy starting in region **E** for changes both in C²–C⁶ and C _{α} –H distances. Thermalized trajectories starting in the **E** region can cross the TS1 transition-state zone TSZ1(D) at shorter C _{α} –H distances (C _{α} –H = 110 pm, C²–C⁶ = 187 pm, C⁷–H = 198 pm, $E \approx 31$ kcal mol^{–1}) or the TS1 transition-state zone TSZ1(conc) at longer C _{α} –H distances (C _{α} –H = 125 pm, C²–C⁶ = 207 pm, C⁷–H = 157 pm, $E \approx 32$ kcal mol^{–1}); these designated regions can be interpreted as either stepwise or concerted pathways. The contours in Figure 1 indicate that within ΔE = 2 kcal mol^{–1} trajectories might go directly to the diradical **D** via TSZ1(D) or to the product region **P** via TSZ1(conc). Clearly, the reaction mechanism can not be addressed without including dynamic effects.

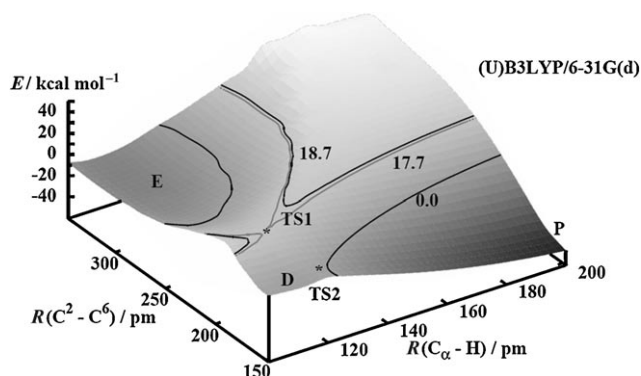


Figure 1. Energy profile for the C²–C⁶ cyclization of **E6** (R¹ = CH₃, R = R² = R³ = H, no benzannulation). Relative energies are given with respect to the energy of **D**. For two fixed distances the energy was optimized with respect to the other degrees of freedom using the TURBOMOLE package.^[18]

We have performed a few “on the fly” trajectory calculations on **E6** supportive of the analysis in the Singleton/Lipton paper.^[12] The smooth energy profile behind TS1 (see Figure 2) supports strongly oscillating trajectories

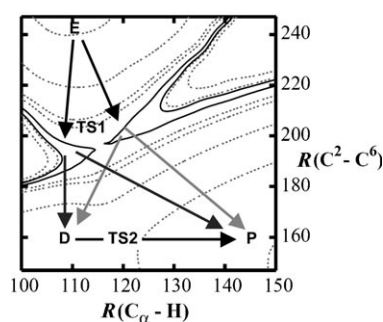


Figure 2. Mechanistic formulation of the thermal ene reaction. The above energy profile (before TS1) urged us to consider a variety of individual thermalized trajectories already starting from the region **E**.

between diradical and productlike structures. Work is in progress to analyze the dynamics based on the potential presented in Figure 1 in more detail using classical and quantum mechanical wave-packet methods.^[17]

We expect that this picture will change appreciably when we consider quantum mechanical computations of enyne allenes with radical-stabilizing substituents, as both the energy of **D** and TSZ1(**D**) may be lowered with respect to TSZ1(conc), and the reaction will proceed in an increasingly stepwise manner. Clearly, for all thermal enyne allene thermolyses studied so far experimentally by KIEs, no single case seems to follow the classical statistical kinetic model. While our experimental data confirm the Lipton/Singleton model,^[12] one has to assume in light of our computational results that the model has to be refined by the assumption of a broad transition-state zone. This suggests that for future dynamic computations on the C²–C⁶ cyclization of enyne allenes, thermalized trajectories starting in region **E** must be considered (Figure 2) and that the analysis must be

performed far in the product region to explain the intramolecular KIEs.

In summary, the present experimental data verify with hindsight the importance of dynamic effects in the thermal C²–C⁶ cyclization of enyne allenes as predicted by Singleton/Lipton through trajectory calculations on the parent enyne allene **E6**. It seems that the influence of substituents in **E1**–**E5** can be explained qualitatively from the dynamic computations on **E6** just by mixing different contributions of “concerted” and “stepwise” trajectories. Hence, radical-stabilizing substituents do lead to large percentage of stepwise trajectories, while other substituents lead to a domination of concerted ones. Future experimental studies on the C²–C⁶ cyclization will further extend the set of data, as additional substituent changes at C¹, C⁷, and even at C³ open the way for additional tests. Our experimental KIEs challenge the theoretical understanding and modeling of nonstatistical kinetic processes, as now a large set of data must be reproduced quantitatively in a consistent theoretical treatment.

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