The Importance of the Ene Reaction for the C^2-C^6 Cyclization of Enyne−Allenes

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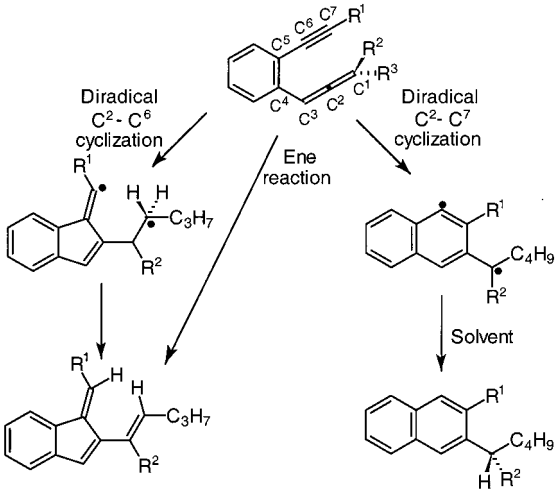
Abstract: The present study establishes the ene reaction as a competing reaction mechanism to the diradical mechanism for the thermal C^2-C^6 cyclization of enyne−allenes which possess bulky substituents at the alkyne terminus. Both reaction routes are found to possess nearly equal free energies of activation. As shown by our computations, primary H/D isotope effects could be used for a definite decision about the mechanism. Concerning the regioselectivity of the cyclization reactions of enyne−allenes our study resolves a long-standing deviation between theoretical results and experimental findings.

1. Introduction

Thermal enyne-(hetero)-allene cyclizations have recently received a lot of attention because their regioselectivity provides an increasing synthetic potential. The regioselectivity was first discovered by Schmittel and co-workers,[1−3] who induced a complete switch from the well-known C^2-C^7 (Myers−Saito) cyclization[4,5] (right-hand side of Scheme 1) to a novel C^2-C^6 cyclization by substituting the hydrogen at the alkyne terminus by an aryl rest (R^1 = Ph) or by a bulky group (R^1 = *t*-Bu, $SiMe_3$). Later, Schmittel, Engels, and co-workers[6,7] found similar reaction switches for enyne−ketene imines and enyne−carbodiimides, showing that the new C^2-C^6 cyclization constitutes a general reaction motif. The regioselectivity of the cyclization is already used in several synthetic routes, e.g. in the synthesis of the kinamycin[8] and the neocryptolepine[9] families or in the preparation of large hydrocarbons.[10,11] Additionally, the reaction is the focus of DNA cleavage[12,13] and photochemical[14] and theoretical studies.[15,16]

Scheme 1. Reaction Scheme of Thermal Cyclization Routes of Enyne−Allenes



The products observed for the new C^2-C^6 cyclization can be explained by a two-step diradical mechanism or by a concerted ene reaction (see Scheme 1). For the alkyne substituent R^1 = Ph, experimental studies suggest a diradical mechanism for the C^2-C^6 cyclization.[17] This is supported by previous theoretical studies[15,18] which computed the switch from the C^2-C^7 cyclization(for R^1 = H) to the C^2-C^6 cyclization (R^1 = Ph) assuming a diradical mechanism for both cyclization paths.[19] One has to keep in mind, however, that the model systems used in previous calculations did not incorporate alkyl substituents (R^2 = *n*-Bu) at the allene terminus and therefore excluded a mechanism via an ene reaction a priori. Consequently, the question whether the C^2-C^6 cyclization proceeds via an ene reaction or via a two-step diradical route is still open.

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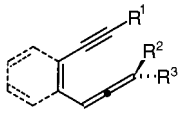
Scheme 2. Summary of the Model Systems Considered in the Present Work[a]



[a] **1**: $R^1 = H$, $R^2 = R^3 = H$, **2**: $R^1 = H$, $R^2 = CH_3$, $R^3 = H$, **3**: $R_1 = Ph$, $R^2 = CH_3$, $R^3 = H$, **4**: $R^1 = t$-Bu, $R^2 = CH_3$, $R^3 = H$. The corresponding benzannulated systems will be abbreviated with **1′**, **2′**, **3′** and **4′**.

This question is of special interest for bulky substituents, because a discrepancy between theory and experiment exists for such groups. While theoretical investigations[18,21] agree with the experimental findings[17] for $R^1 = Ph$, they did not reproduce the switch to the C^2-C^6 cyclization if $R^1 = H$ was replaced by bulky substituents ($R^1 = t$-Bu, $SiMe_3$). This deviation between theoretical and experimental findings could result from the chosen model system or it could be that the ene reaction is favored before the diradical mechanism for these bulky substituents. The first argument is supported by a recent study of Wenthold and Lipton,[22] who showed for the simplest system ($R^1 = R^2 = R^3 = H$, see Scheme 2) that for the diradical mechanism benzannulation decreases the difference between the transition state energies of the C^2-C^6 and the C^2-C^7 cyclization. In this study, unfortunately, no explicit reaction barriers were given, so that it is not possible to judge whether benzannulation actually lowers or raises the activation barriers for the C^2-C^6 and the C^2-C^7 cyclization, respectively. In this work we therefore want to provide additional insight into this topic originally investigating the influence of benzannulation in combination with substituent effects.

Both questions, the discrepancy between experiment and theory for $R^1 = t$-Bu or $SiMe_3$ and the relevance of the ene mechanism for the C^2-C^6 cyclization of enyne−allenes, are investigated in the present work. For the latter we compare the reaction barriers computed for the different reaction paths as a function of the substituents depicted in Scheme 2, namely $R^1 = H$, $R^2 = CH_3$, $R^3 = H$ (**2**), $R^1 = Ph$, $R^2 = CH_3$, $R^3 = H$ (**3**), and $R^1 = t$-Bu, $R^2 = CH_3$, $R^3 = H$ (**4**). Since benzannulation could be the reason for the discrepancy discussed above, the benzannulated derivatives **2′**, **3′**, and **4′** are included in the comparison. Additionally, we investigate the primary kinetic H/D isotope effects for all routes, which will help to verify the present theoretical findings by means of a kinetic study.

2. Computational Aspects

Density Functional Theory (DFT)[23−25] is a reliable tool for the description of a reaction path as long as the system possesses a closed shell electronic structure along the whole reaction path. Examples are Diels−Alder reactions[26,27] and the ene reaction.[28,29] If the system develops a diradical character along the reaction path, DFT can only be used for such parts in which the system possesses mostly closed shell character, because the error bars of DFT for diradical systems are quite large.[15] Whether DFT can be employed or not can be seen in an unrestricted approach in which an increasing diradical character of the system can be estimated from the increasing spin-contamination of the wave function. Since the diradical mechanisms of the C^2-C^6 and the C^2-C^7 cyclization (see Scheme 1) are processes which lead to a diradical intermediate, DFT can only be used to describe such regions of both reaction paths where the wave function resembles the reactant wave function, i.e., possesses mostly closed shell character. Fortunately, in the diradical mechanism of the C^2-C^6 and the C^2-C^7 cyclization the diradical character develops only shortly after the transition states so that DFT is sufficiently accurate (see Table 1 and dicussion below) to determine both reaction barrier heights.[15] Consequently, in the present work DFT was employed to compare the reaction barriers of the various mechanisms.

Table 1. Evaluation of Computational Methods for Model System **1** and **2**[g]

level of theory	path A	path B	path C
	1		
UB3LYP/6-31G(d)[a]	+31.4		+24.0
UBLYP/6-31G(d)[b]	+31.5		+20.2
UBPW91/6-31G(d)[b]	+28.6		+18.0
RCCSD(T)/cc-pVDZ[c]	+35.0		+22.2
experiment[d]	n.a.		+23.3 ± 1
	2		
UB3LYP/6-31G(d)	+30.7	+29.9	+23.7
UB3LYP/6-311G(2df,2pd)[e]	+33.4	+32.5	+26.2
UBPW91/6-31G(d)	+24.2	+22.1	+17.6
UBPW91/6-311G(2df,2pd)[f]	+26.3	+23.7	+19.4
RCCSD(T)/cc-pVDZ[e]	+29.0	+29.5	+22.4

[a] Reference 15. [b] Reference 16. [c] Reference 16. Geometry and correction to Gibbs free energy obtained at the UBLYP/6-31G(d) level of theory. [d] Suggested by Myers.[50] [e] Single point energy based on UB3LYP/6-31G(d) geometry. [f] Single point energy based on UBPW91/6-31G(d) geometry. [g] All $\Delta G^{\ddagger}_{298}$ values are given in kcal/mol. A description of routes A, B, and C is given in the text.

DFT computations were performed with the B3LYP[30,31] and the BPW91[32,33] functional in connection with the 6-31G(d)[34−36] basis set. The latter functional was employed because it should give the best description for diradical systems.[37] To avoid uncertainties due to developing diradical characters a spatial and spin unrestricted ansatz in the following denoted as UB3LYP and UBPW91 were employed. An additional check of the stability of the wave functions was performed[38,39] and the wave function as well as the geometry were reoptimized if an instability was encountered. This additional check of the wave function is necessary since in many cases the simple use of the unrestricted approach does not reveal an existing instability if the iterative solution of the Kohn−Sham equations starts from a closed shell wave function. Corrections to the pure singlet state were not performed since all optimized stationary points under consideration possess no or only small spin contaminations ($\langle S^2 \rangle < 0.2$).

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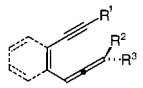
Table 2. Energies, Enthalpies, and Free Energies of Activation for the Calculated Model Systems and Reaction Pathways **A**, **B**, and **C**[a]

system		C^2-C^6 cyclization						C^2-C^7 cyclization		
		route A			route B			route C		
		$\Delta E^{\ddagger}$	$\Delta H^{\ddagger}_{298}$	$\Delta G^{\ddagger}_{298}$	$\Delta E^{\ddagger}$	$\Delta H^{\ddagger}_{298}$	$\Delta G^{\ddagger}_{298}$	$\Delta E^{\ddagger}$	$\Delta H^{\ddagger}_{298}$	$\Delta G^{\ddagger}_{298}$
1[b]	$R^1 = H$; $R^2 = R^3 = H$	+30.8	+29.0	+31.4				+22.4	+21.4	+24.0
2	$R^1 = H$; $R^2 = CH_3$; $R^3 = H$	+30.2	+28.4	+30.7	+29.0	+26.1	+29.9	+22.2	+21.2	+23.7
2′	$R^1 = H$; $R^2 = CH_3$; $R^3 = H$	+29.7	+27.8	+29.7	+26.5	+23.8	+27.4	+24.0	+23.0	+25.3
3	R1 = Ph; $R^2 = CH_3$; $R^3 = H$	+26.6	+24.9	+26.5	+27.7	+25.8	+28.2	+27.6	+26.2	+29.0
3′	$R^1 = Ph$; $R^2 = CH_3$; $R^3 = H$	+24.9	+23.0	+24.4	+25.5	+23.6	+26.0	+30.0	+28.6	+31.3
4	$R^1 = t$-Bu; $R^2 = CH_3$; $R^3 = H$	+32.1	+30.0	+32.2	+31.1	+28.6	+32.3	+28.9	+27.5	+31.1
4′	$R^1 = t$-Bu; $R^2 = CH_3$; $R^3 = H$	+31.0	+29.0	+30.6	+29.2	+26.6	+30.4	+31.4	+29.8	+32.8

[a] Route A denotes the reaction route initiated by the rotation of the methyl group $C'H_3$ (see Figure 1) away from C^7, while route B is the reaction obtained from the opposite direction of rotation. Route C corresponds to the diradical C^2-C^7 cyclization. For **2**, **2′**, **4**, and **4′** route B corresponds to an ene reaction, while **3** and **3′** follow a diradical pathway. [b] Reference 15.

Optimized stationary points[40] were characterized as minima or transition states by the computation of the corresponding vibrational frequencies. Transition states for the ene reaction have been confirmed by an analysis of the intrinsic reaction coordinate path (IRC). Transition states of diradical pathways were analyzed by the vector of the negative imaginary frequency since IRC calculations for these mechanisms follow the closed shell potential energy surface and lead to a zwitterion instead of the energetically more favorable diradical intermediate. The zero-point energies (ZPE) used to obtain $\Delta H^{\ddagger}_{298}$ and $\Delta G^{\ddagger}_{298}$ are based on the force constants computed at the DFT/6-31G(d) level of theory. The influence of the nuclear motion and temperature effects were incorporated in the standard approach.[41] The calculations were performed with the Gaussian98[42] and the MOLPRO package.[43]

To check the accuracy of our computations more sophisticated approaches were used for the model system **2**. RCCSD(T)[44−47] calculations employing a *cc*-pVDZ basis set[48] were performed to test the reliability of the functionals. The suitability of the RCCSD(T) method was checked by the T_1 diagnostic. Additionally, single-point DFT calculations employing UB3LYP/6-31G(d) and UBPW91/6-31G(d) geometries and the 6-311G(2df,2pd)[34−36] basis set were performed to estimate the influence of larger basis sets. All results are summarized in Table 1. Table 1 clearly shows that the UB3LYP and the RCCSD(T) results agree nicely with each other and with the data available for **1**,[15,16] while the UBPW91 functional seems to underestimate all free energies of activation by 6−7 kcal/mol. Differences between the UBPW91 and the other approaches are also found if the relative heights of the barriers are taken into consideration. While RCCSD(T) and UB3LYP compute the difference between the barrier of path B and path C to be 6−7 kcal/mol, the UBPW91 functional predicts a difference of only 4−5 kcal/mol. Path A denotes the diradical C^2-C^6 cyclization, when the methyl group of **2** is rotated away from C^7 (see Scheme 2 and Figure 2), while path B represents the opposite direction of rotation with both, a diradical and a concerted ene reaction, being possible. For **2**, however, path B uniquely corresponds to a transition state for an ene reaction. Finally, path C corresponds to the diradical C^2-C^7 cyclization. While the difference between paths B and C seems to be underestimated by the UBPW91 functional the difference between paths A and B seems to be slightly overestimated, however, all approaches agree that this difference is much smaller than the difference between paths A and C or B and C. With the improved basis set both functionals predict higher barriers for all reactions, the difference between the various barriers, however, is nearly not altered. In summary, Table 1 underlines that for the goals of the present work the UB3LYP/6-31G(d) approach represents a suitable ansatz.

3. Results and Discussion

Table 2 summarizes the energetical data which were computed to compare the various reaction paths. For **3′** and **4′** the geometrical structures of the TS of the diradical mechanism of the C^2-C^6 cyclization and the ene reaction are sketched in Figure 1. Selected geometrical parameter can be taken from Table 3. For model system **4′** the course of the different mechanisms is depicted in Figure 2. All absolute energies and the structures of all stationary points are available as Supporting Information.[49]

Both the diradical and the ene mechanism of the C^2-C^6 cyclization are initiated by a rotation around the terminal allene double bond (C^1-C^2 bond, see Figure 2). If the CH_3 group is rotated away from the alkyne terminus (e.g. path A in Figure 2), only the diradical mechanism of the C^2-C^6 cyclization can take place. It consists of two steps. In its first step the short-lived diradical **A** (see Figure 2) is obtained in which the new C^2-C^6 bond is already formed. It represents a (σ,π)-diradical with the radical centers mainly located at C^1 and C.[7] The second step of the diradical mechanism yields the final product. It is obtained either through an internal H-shift which had to be initiated by an internal rotation around the C^1-C^2 single bond

(40) For the determination of the transition states for the diradical C^2-C^6 and the C^2-C^7 cyclization, automized transition state optimizers (e.g. the QST2 or QST3 routines implemented in *Gaussian98*) cannot be used, since within these computations the instability of the wave function is not encountered without additional checks (see text). This can lead to artifactual reaction barriers and geometries of the TS. For the diradical C^2-C^6 cyclization of **4′** (route **A**) the automatic optimizer computed a TS having a slightly higher energy of activation (1 kcal/mol) and a substantially shortened (10 pm) C^2-C^6 distance (see Figure 1) than obtained with a manual search following the C^2-C^6 ring closure.

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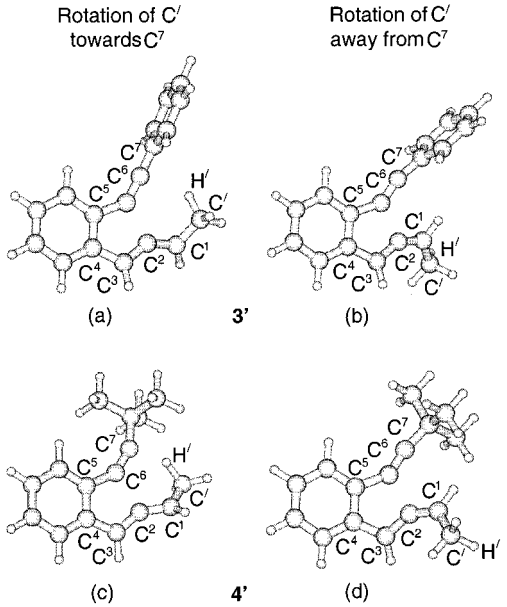

Figure 1. Transition states for the C^2-C^6 cyclization of **3′** and **4′** (for further explanation see Table 3 and text).

Table 3. Selected Geometrical Parameters of the Transition States for the C^2-C^6 Cyclization of **3′** and **4′**

	3′		**4′**	
parameter	TS **a**	TS **b**	TS **c**	TS **d**
d(C′H′)	1.108	1.099	1.190	1.100
d(H′C^7)	2.300	4.881	1.720	5.284
d(C^2C^6)	1.911	1.904	1.979	1.880
d(C^1C′)	1.485	1.503	1.448	1.504
d(C^1C^2)	1.352	1.339	1.361	1.337
d(C^2C^3)	1.357	1.366	1.339	1.365
d(C^3C^4)	1.444	1.442	1.454	1.443
d(C^4C^5)	1.414	1.420	1.414	1.419
d(C^5C^6)	1.463	1.456	1.458	1.463
d(C^6C^7)	1.261	1.260	1.263	1.254
∠C^2C^1C′	123.4	235.3	119.4	235.4
∠$C^3C^2C^1$	141.3	143.1	147.8	142.2
∠$C^5C^6C^7$	138.0	142.5	146.0	141.9
∠$C^6C^7R^1$	174.9	196.1	169.9	205.1
∠C′$C^1C^2C^3$	−153.5	+22.8	−147.2	+19.0
∠C′$C^1C^2C^3$	16.2	25.4	16.4	31.1

[a] For a definiton of the abbreviations see Figure 1 (angles in deg, distances in Å).

or from hydrogen abstraction reactions with the solvent. Attempts to trap the diradical intermediate by radical scavengers failed so far.[17] This supports the assumption that the diradical formation is the rate-determining step. Consequently, in the present work only the first step of the diradical mechanism is considered.

If the CH_3 group is rotated toward the alkyne terminus (e.g. path B in Figure 2) the cyclization can proceed via a diradical or an ene mechanism. In the ene reaction, both the formation of the new C^2-C^6 bond and the H-shift occur in one step. This means that the reaction path of the ene mechanism possesses only one transition state (TS). If the formation of the new C^2-C^6 bond and the hydrogen shift take place at the same time the reaction is designated as a concerted synchronous ene reaction, while it is labeled as a concerted asynchronous ene reaction[27,29] if both processes take place one after the other without the occurrence of any intermediate. Along path B a diradical mechanism cannot be excluded a priori (not indicated in Figure 2). For a diradical mechanism it is necessary that the emerging diradical, which already contains the newly formed C^2-C^6 bond, is stabilized to an extent that it represents a local minimum on the PES. Furthermore, the TS which leads to this intermediate has to be energetically favorable with respect to the TS of the ene reaction. In the diradical mechanism the final H-shift proceeds over a second transition state. In difference to the diradical reaction path discussed above, an internal H-shift does not have to be initiated by an internal rotation around the C^1-C^2 bond. As for path A it can be assumed that the building process of the diradical intermediate is the rate-determining step.

The C^2-C^7 (Myers−Saito) cyclization (e.g. path C of Figure 2) is also initiated by a rotation around the terminal allene double bond, but in difference to the C^2-C^6 cyclization the CH_3 group can only be rotated away from the alkyne terminus due to strong steric interaction between the terminal substituents of the alkyne and of the allene group, respectively.

Let us first concentrate on the systems with R^1 = Ph (**3** and **3′** in Scheme 2). Previous computations could reproduce the experimentally established C^2-C^6 cyclization if a diradical pathway was assumed. It is unclear, however, if the mechanism of the ene reaction can compete with the diradical route. For **3**, as well as for **3′**, our computations predict a diradical mechanism for the C^2-C^6 cyclization along *both* pathways A and B, i.e., also if the CH_3 group is rotated toward the alkyne terminus only the TS of a diradical mechanism could be located. The nature of this TS (see Figure 1, a) can be seen from the mode possessing a negative imaginary frequency. The nuclear motion connected with this mode solely closes the five-membered ring, i.e., points to a diradical intermediate **A** (see Figure 2). Attempts to locate the TS of the ene reaction failed, indicating that it represents a saddle point of higher order. For **3** (R^1 = Ph, R^2 = CH_3, R^3 = H) the computed activation energy ($\Delta E^{\ddagger}$) is about 28 kcal/mol, if the CH_3 group is rotated toward the alkyne group (**B**) and 27 kcal/mol for the opposite direction of rotation (**A**). These values are close to the activation energy that was calculated for the model system containing R^1 = Ph, R^2 = R^3 = H (27 kcal/mol).[18] The good agreement is expected because the CH_3 group should not change the barrier height for the diradical mechanism considerably. For the C^2-C^7 cyclization we predict a $\Delta E^{\ddagger}$ of 28 kcal/mol. As expected, this $\Delta E^{\ddagger}$ is equal to the activation energy computed for the model system (R^1 = Ph, R^2 = R^3 = H).[18] Since the energetic differences between the TS of both cyclization modes do not change considerably if one goes from $\Delta E^{\ddagger}$ to $\Delta H^{\ddagger}_{298}$ or $\Delta G^{\ddagger}_{298}$, the activation barriers for both cyclization modes differ only slightly. A major difference arises if the influence of the benzannulation is taken into account. Going from **3** to **3′** the barrier height of the C^2-C^6 cyclization decreases by about 2 kcal/mol, while the barrier height of the C^2-C^7 cyclization increases by about the same amount. As a consequence, for **3′**, which resembles the experimentally investigated system more than **3**, our computation predicts a preference of about 7 kcal/mol in the free energy of activation for the C^2-C^6 over the C^2-C^7cyclization. This explains why only the five-membered-ring cyclization was observed within the experiment.

It is found experimentally that the switch from the C^2-C^7 to the C^2-C^6 cyclization is also induced from bulky substituents at the alkyne terminus, e.g. from R^1 = *t*-Bu or $SiMe_3$.[12] Under the assumption of a diradical pathway previous computations did not find this switch. A reason for the discrepancy could be that the mechanism of the ene reaction, which was not considered in the previous work, possesses a much smaller reaction barrier than the diradical mechanism. To investigate this problem, calculations were performed for model systems **4** and **4′**. Indeed, for path B (rotation of the CH_3 group toward

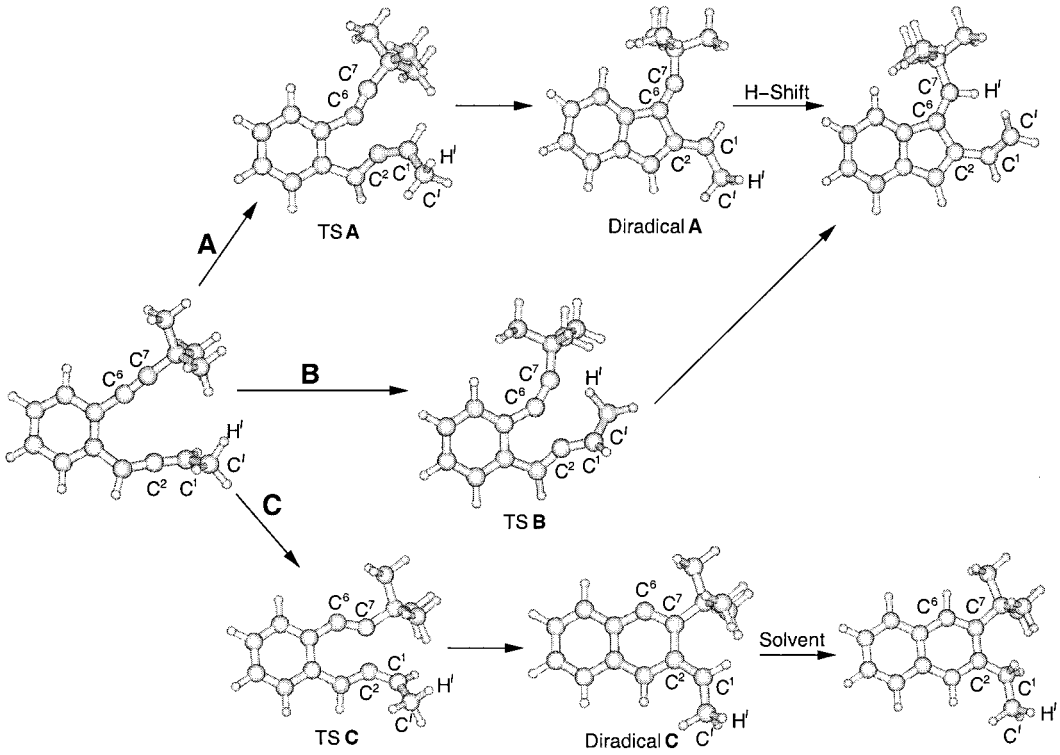

Figure 2. Calculated transition states, intermediates, and products of the thermal cyclization of enyne−allene **4′**. Path **A**: Diradical C^2-C^6 cyclization. Path **B**: Alternative C^2-C^6 cyclization mechanism via an ene reaction. Path **C**: C^2-C^7 cyclization via a diradical mechanism.

the alkyne terminus) of **4** our computation solely predicts an ene mechanism. Along the computed intrinsic reaction coordinate (IRC) path the movement of the hydrogen H′ from the CH_3 group to $C^7$and the closure of the five-membered ring (formation of the C^2-C^6 bond) happen in a concerted, but asynchronous manner, with the shift of H′ precedent to the ring closure. The free energy of activation for the ene reaction is about 32 kcal/mol. Along path B of **4** we could not locate a TS for a diradical mechanism. Along path A solely the diradical mechanism can take place. Our computations predict a free energy of activation ($\Delta G^{\ddagger}_{298}$) of 32 kcal/mol, i.e., we find that both the ene reaction (along path B) and the diradical mechanism (along path A) possess equal reaction barrier heights. However, for **4** our computations still favor the C^2-C^7 cyclization because the computed activation energy of the C^2-C^7 cyclization ($\Delta E^{\ddagger} = 29$ kcal/mol, $\Delta H^{\ddagger}_{298} = 28$ kcal/mol, $\Delta G^{\ddagger}_{298} = 31$ kcal/mol) is still lower than that of the C^2-C^6 cyclization (routes A and B).

The switch from a C^2-C^7 cyclization to a C^2-C^6 cyclization is predicted if benzannulation is taken into account. Going from **4** to **4′**, the barrier height of both C^2-C^6 cyclization mechanisms A and B decreases by about 1 kcal/mol, while the activation energy of the C^2-C^7 cyclization C increases by about 2 kcal/mol. As a consequence the free energy of activation for the C^2-C^6 cyclization is about 31 kcal/mol ($\Delta G^{\ddagger}_{298} = 30.6$ and 30.4 kcal/mol for the diradical and the ene mechanism, respectively), while the free energy of activation for the C^2-C^7 cyclization is about 33 kcal/mol, i.e., about 2 kcal/mol higher.[51] This resolves the discrepancy between theory and experiment, which existed since the benzannulation of the experimentally investigated compounds was neglected in the model systems considered in the previous work.[18]

For the C^2-C^6 cyclization reaction along path B (rotation of the terminal CH_3 group toward the alkyne moiety) we predict different reaction mechanisms for **3′** and **4′**, respectively. This must result from differences in the interaction between the substituent at C^7 (R^1 = Ph for **3′** and R^1 = *t*-Bu for **4′**, respectively) and the neighboring centers. This difference is already noticeable in the geometrical stuctures of both TSs given in Figure 1, structures **a** and **c**. Structure **a** of Figure 1 depicts the TS of the diradical cyclization pathway which was found for **3′**, while **c** shows the TS of the ene reaction which was computed for **4′**. The different natures of both TSs can best be seen from the distance between H′ and C^7 (Table 3). This distance is predicted to be 2.3 Å for TS **a**. The much shorter distance (1.72 Å) which we computed for TS **c** indicates that the hydrogen shift from C^2 to C^7 has already started. This is also seen from the length of the C′−H′ bond. While it is already considerably elongated in **c** ($d_{C'H'} = 1.19$ Å), it represents a more or less normal C−H bond for **a** ($d_{C'H'} = 1.108$ Å). The different natures of both TSs is also expressed in the distance between C^2 and C^6 which is smaller for TS **a** (1.911 Å) than for TS **c** (1.979 Å). Another indication that TS **c** leads directly to the fulvene while TS **a** leads to a diradical intermediate is the difference in the C^1-C' bond length (1.485 Å for TS **a** and 1.448 Å for TS **c**). This bond represents a double bond in the fulvene, but is still a single bond in the diradical intermediate. The TSs which are obtained if the CH_3 group is rotated away from the alkyne terminus are depicted in Figure 1, structures **b** and **d**. Since both structures are TSs for diradical routes, the differences are much smaller than those discussed for structures **a** and **c** of Figure 2.

While our computations favor a C^2-C^6 cyclization for **4′**, i.e., resolve the disrepancy to the experiment, they cannot decide whether the ene or the diradical mechanism takes place because

(50) Myers, A. G.; Dragovich, P. S.; Kuo, E. Y. *J. Am. Chem. Soc.* **1992**, *114*, 6369−6386.

(51) An estimate on the influence of solvent effects on the reaction barriers for **4′** was performed on the UB3LYP/6-31G(2df,2pd)//UB3LYP/6-31G(d) level of theory in conjuction with the COSMO model.[52] The reaction barriers do not alter significantly ($\Delta E^{\ddagger} = 31.0$ kcal/mol for **A**, +28.6 kcal/mol for **B** and +31.5 kcal/mol for **C**). This result validates the reliability of gas-phase calculations.

Table 4. Influence of the Deuteration of the Methyl Group ($C'H_3$) [kcal/mol]

H/D	path	ν [cm^{-1}]	T [K]	$\Delta H^{\ddagger}_{298}$	$\Delta G^{\ddagger}_{298}$
		2 (UB3LYP/6-31G(d))			
H	A	−711	298.15	+28.4	+30.7
	B	−695	298.15	+26.1	+29.9
	C	−470	298.15	+21.2	+23.7
D	A	−711	298.15	+28.4	+30.8
	B	−651	298.15	+26.6	+30.4
	C	−470	298.15	+21.2	+23.7
		4′ (UB3LYP/6-31G(d))			
H	A	−878	298.15	+29.0	+30.6
	B	−562	298.15	+26.6	+30.4
	C	−883	298.15	+29.8	+32.8
D	A	−878	298.15	+29.0	+30.6
	B	−536	298.15	+26.9	+30.8
	C	−883	298.15	+29.8	+32.8

the computed difference is far too small for a definitive decision. To check whether steric effects favor one of both pathways we also investigated systems **2** and **2′**. Due to R^1 = H instead of R^1 = *t*-Bu the steric demand should be smaller for this system. Indeed, as can be seen from Table 2, steric interaction seems to be somewhat smaller for the ene reaction. Its free energy of activation drops by about 3 kcal/mol while that of the diradical pathways decreases only by about 1 kcal/mol. Unfortunately, this finding cannot be proved experimentally, because the activation energy of the C^2-C^7 cyclization is considerably lower for **2** and **2′**.

If, besides an alkyl substituent at R^2, a bulky substituent is inserted at R^3 (Scheme 2) the barrier of the diradical pathway should increase more than the barrier of the ene reaction, because this substituent is moved toward R^1 along the diradical route while it is moved away in the case of the ene reaction. Considering such steric effects on the basis of the TS geometry computed for **4′** it is plausible to expect that the C^2-C^6 cyclization will proceed via an ene reaction for the system used in the experiment (R^1 = $PO(Ph)_2$, R^2 = *n*-Bu, R^3 = *t*-Bu). A proof on the basis of calculated reaction barriers, however, is computationally not feasible due to the size of the system and the accuracy needed for a reliable prediction.

While a distinction between both mechanisms on the basis of a computational approach is not possible to date, a kinetic study should give a definitive answer on the basis of primary H/D isotope effects. Differences between both mechanisms arise, because within the mechanism of the ene reaction the hydrogen center H′ is shifted from C′ to C^7 while during the rate-determining step of the diradical mechanism only the new C^2-C^6 bond is formed, i.e., all C−H bonds are nearly unaltered. Computed H/D isotope effects for the systems **2** and **4′** are given in Table 4. Table 4 clearly shows that a deuteration of the methyl group at the allene terminus does not affect the free energy of activation for the diradical reaction paths A and C. For the ene reaction of **2** a primary isotope effect k_H/k_D[53−55] of 2.32 is calculated. The effect results since for the TS of path B the imaginary frequency of the C′−H′ streching mode changes from *i*695 cm^{-1} to *i*651 cm^{-1}. For the ene mechanism of system **4′** k_H/k_D is computed to be 1.97. Consequently, an experimental measurement of the isotope effects will give valuable information about the nature of the C^2-C^6 cyclization mechanism. The values computed for the present reactions are similar to the ones found experimentally for various other ene reactions (k_H/k_D = 2.1−2.7).[56,57,58]

4. Summary

In the present study we could show that for the C^2-C^6 cyclization of enyne−allene compounds the ene reaction represents a competitive mechanism to the diradical pathway. The only exceptions are systems with substituents at the alkyne terminus which are able to stabilize the evolving radical center at C^7. An example are systems with R^1 = Ph (**3** and **3′**). For these systems we only can locate a TS for the diradical mechanism. For all other substituents at the alkyne terminus, e.g. R^1 = H (**2** and **2′**) or *t*-Bu (**4** and **4′**), both possible mechanisms for the C^2-C^6 cyclization possess nearly identical barrier heights. In systems in which R^1 and R^3 (Scheme 2) are substituted by bulky groups, the ene reaction should possess a lower barrier than the diradical mechanism since both bulky substituents are rotated away from each other in the course of the ene reaction, while they are rotated toward each other along the diradical pathway. This consideration suggests that the C^2-C^6 cyclization might proceed via an ene raction for the molecule which was actually investigated in the experiment (R^1 = *t*-Bu, R^2 = *n*-Bu, R^3 = $POPh_2$). However, a proof, which is solely based on theory, is impossible to date due to the size of the system and the subtle effects which have to be taken into consideration. A final answer to the question of which mechanism takes place could be given by an experimental determination of the isotope effect k_H/k_D of the reaction. This is shown by the present investigation which computed k_H/k_D to be 1.97 for the ene reaction of **4′**. For the diradical mechanism no isotope effect is found in the calculations.

In addition, the present study resolves an existing deviation between theory and experiment concerning the regioselectivity of the cyclization of enyne−allenes. While the switch from the C^2-C^7 to the C^2-C^6 cyclization was experimentally found for bulky substituents, previous computations predicted a C^2-C^7 cyclization. Our calculations reveal that the benzannulation (Scheme 2) represents the key for the understanding of this discrepancy. While we predict the C^2-C^7 cyclization for **4**, the reaction barriers computed for the more appropriate model system **4′** clearly reflect the experimental finding (C^2-C^6 cyclization). Nevertheless, it has already been discussed above that we cannot decide whether the ene reaction or the diradical mechanism (or both) takes place. As shown by the computed primary H/D isotope effects, this answer could be given by means of a kinetic study.

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Supporting Information Available: Absolute energies and structures of all stationary points for compounds **2** to **4′** in Cartesian coordinates (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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