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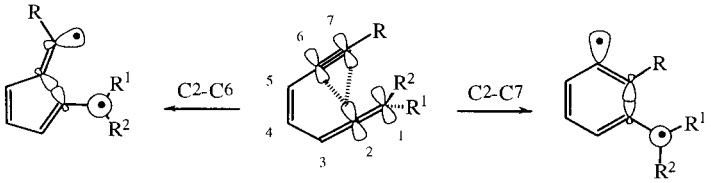
Regioselectivity of Biradical Cyclizations of Enyne-Allenes: Influence of Substituents on the Switch from the Myers – Saito to the Novel $C^2 - C^6$ Cyclization**

Bernd Engels,* Christian Lennartz, Michael Hanrath, Michael Schmittel,* and Marc Strittmatter

The Myers – Saito $C^2 - C^7$ cyclization of enyne-allenes[1] has recently received a lot of attention owing to the involvement of the α,3-didehydrotoluene biradicals (Scheme 1) in DNA-cleavage reactions[2] and subsequent reactions of synthetic interest.[3]

The synthetic potential of thermal enyne-allene reactions was extended when Schmittel and co-workers found a complete switch from the Myers – Saito $C^2 - C^7$ cyclization to a $C^2 - C^6$ cyclization (Scheme 1).[4] For different groups R^1 and R^2, the new $C^2 - C^6$ cyclization takes place if the terminal hydrogen atom of the alkyne group (R = H) is replaced by an aryl group (R = Ph) or by sterically bulky groups (e.g., R = *t*Bu, $SiMe_3$). Later Gillmann et al.[5] and Rodriguez et al.[6] found a similar reaction switch, which indicates that the new $C^2 - C^6$ cyclization constitutes a general reaction motif.



1 – 4

Scheme 1. Thermal reaction of enyne-allenes: $C^2 - C^6$ cyclization (left) and Myers – Saito $C^2 - C^7$ cyclization (right). **1**: R = H, **2**: R = Ph, **3**: R = *t*Bu, **4**: $R = NH_2$; $R^1 = R^2 = H$.

As indicated on the right-hand side of Scheme 1, the rate-determining step of the Myers – Saito reaction is the formation of a (σ,π) biradical. Experimental studies[7, 8] on the new $C^2 - C^6$ cyclization (shown on the left-hand side of Scheme 1) also suggest that biradical formation is the rate-determining step, but the final proof for a biradical intermediate was missing so far. Although the switch from the $C^2 - C^7$ to the $C^2 - C^6$ cyclization is experimentally well established, the reasons are still unclear.

In the present investigation quantum-chemical calculations[9] address for the first time the regioselectivity of biradical cyclizations in enyne-allenes with different substituents—namely, R = H (**1**), Ph (**2**), *t*Bu (**3**), and NH_2 (**4**)—at the alkyne terminus (with $R^1 = R^2 = H$). In addition, the hitherto postulated biradical intermediate of the $C^2 - C^6$ cyclization could be trapped by hydrogen transfer, thus providing the most direct proof of its biradical nature.

The theoretical results are summarized in Table 1, and the optimized geometrical structures of the reactants and of the transition states are shown in Figure 1. We will first compare

Table 1. Summary of the theoretical data. Energy differences are given with respect to the reactants (in kcal mol^{-1}). Thermochemical corrections were made at a temperature of 298 K.

		R = H	R = Ph	R = *t*Bu	R = NH_2
$C^2 - C^7$ cyclization					
TS[a]	$R_{C^2-C^7}$[c]	2.07	2.06	2.07	2.08
	$\Delta E^{\neq}$	22.4	28.0	29.0	20.9
	$\Delta H^{\neq}$	21.4	26.7	27.9	19.8
	$\Delta G^{\neq}$	24.0	29.8	31.1	22.7
product[b]	$R_{C^2-C^7}$[c]	1.43	1.41	–	1.50
	ΔE_r	– 21.3	– 23.3	–	– 34.7
$C^2 - C^6$ cyclization					
TS[a]	$R_{C^2-C^6}$[c]	1.90	1.96	1.90	2.13
	$\Delta E^{\neq}$	30.8	27.2	33.0	16.9
	$\Delta H^{\neq}$	29.0	25.1	31.4	15.4
	$\Delta G^{\neq}$	31.4	28.7	33.3	17.8
product[b]	$R_{C^2-C^6}$[c]	1.51	1.50	–	1.47
	ΔE_r	12.0	1.3	–	– 37.0

[a] DF(B3LYP) in combination with a 6-31G* basis set. TS = transition state. [b] MR-CI in combination with a DZP basis set. [c] Distance in Å.

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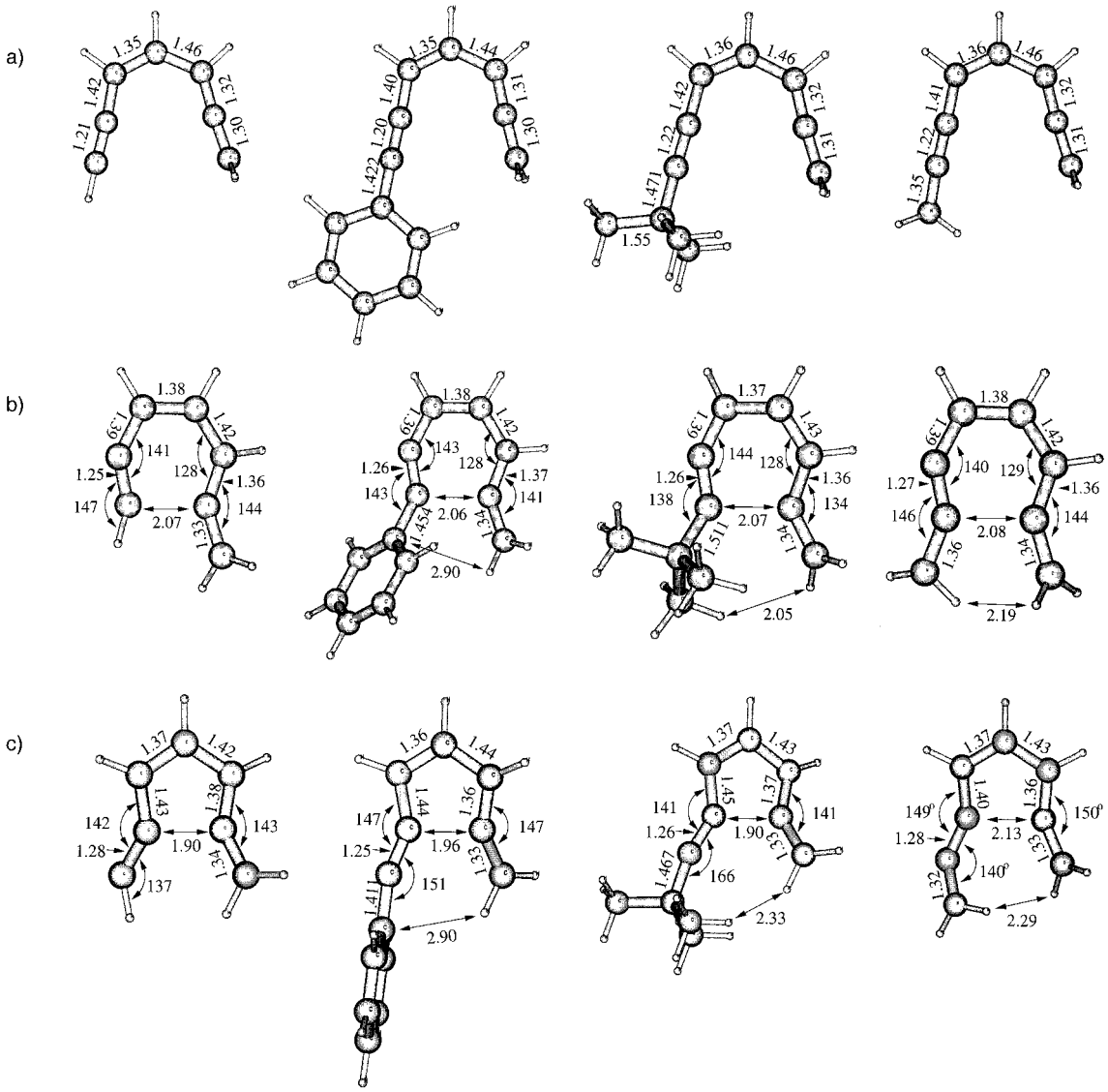
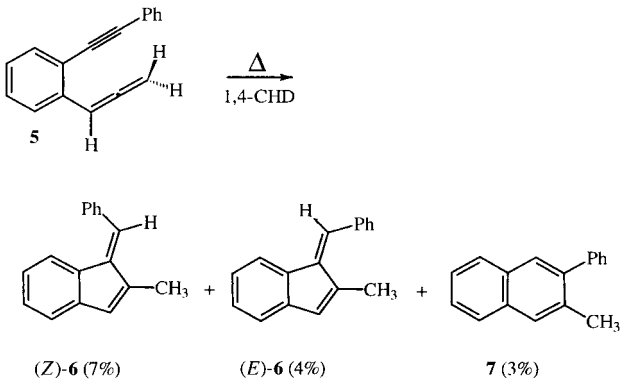


Figure 1. Geometry-optimized (DFT/6-31G*) structures of the reactants of the thermal biradical cyclization of the enyne-allenes **1**–**4**. a) Reactants; b) transition states for the Myers–Saito reaction; c) transition states for the new C^2-C^6 cyclization. Selected distances [Å] and angles [°] are given.

the results for **1** (R = H) and **2** (R = Ph).[10] While the activation energy of the C^2-C^7 cyclization increases by about 6 kcal mol^{-1} if the terminal hydrogen atom in **1** is replaced by a phenyl ring (**2**), the activation energy of the C^2-C^6 cyclization falls by about 3 kcal mol^{-1}. As a result, the computed reaction barrier to the C^2-C^6 cyclization for **2** ($\Delta G^{\ddagger} \approx 29$ kcal mol^{-1}) is somewhat smaller than that of the C^2-C^7 cyclization ($\Delta G^{\ddagger} \approx 30$ kcal mol^{-1}).

The calculated slight preference for the C^2-C^6 cyclization was confirmed experimentally by the thermolysis of the novel enyne-allene **5** (Scheme 2). When **5** was heated for 18 h in neat 1,4-cyclohexadiene, the benzofulvene derivatives (*Z*)-**6** (7%) and (*E*)-**6** (4%) were formed along with the C^2-C^7 cyclization product **7** (3%). Clearly (*Z*)-**6** and (*E*)-**6** are both derived from the corresponding fulvene biradical (Scheme 1) through hydrogen abstraction, which constitutes the strongest proof thus far for the biradical nature of the C^2-C^6 cyclization.

An analysis of the theoretical data reveals that the differences in the activation energies between **1** and **2** result from



Scheme 2. Preferential formation of the products during the thermolysis of **5**. 1,4-CHD = 1,4-cyclohexadiene.

electronic interactions between the alkyne group and the phenyl ring. The bond distance between C^7 and the phenyl ring in **2** is 1.422 Å. In the transition state of the C^2-C^7 cyclization this bond is elongated to 1.454 Å, while it is

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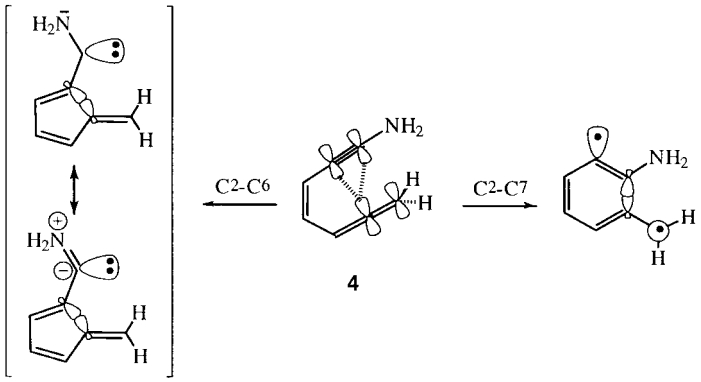
shortened to 1.411 Å in the transition state of the C^2-C^6 cyclization. This indicates that the mesomeric interaction between the alkyne group and the phenyl ring strengthens along the reaction path of the C^2-C^6 cyclization, but weakens along the Myers–Saito pathway. Clearly a stabilization of the emerging radical center through mesomeric interactions at the alkyne terminus is only possible for the C^2-C^6 cyclization, where the vinyl radical center develops in the position α to the phenyl ring. No mesomeric stabilization between the radical center and the phenyl group is possible in the C^2-C^7 cyclization.

Steric interactions are unimportant in both cyclizations of **2** ($R^1=R^2=H$), because in both transition states the orientation of the phenyl ring permits large distances between the two terminal groups (Figure 1b, c). However, since the experimental preference for the C^2-C^6 cyclization of substituted enyne-allenes (R^1, $R^2 \neq H$) is much more pronounced than in **2**,[4] steric effects between the substituents of the alkyne and allene termini are apparently relevant.

Indeed, steric effects can be detected by calculations in a comparison of the cyclization of **1** (R = H) and **3** (R = *t*Bu). Substitution of H by *t*Bu leads to an increase in the activation energies of both reactions. Although the increase for the C^2-C^7 cyclization (ca. 7 kcal mol^{-1}) is much larger than for the C^2-C^6 cyclization (ca. 2 kcal mol^{-1}), the C^2-C^7 cyclization still possesses a smaller activation energy. At first this finding seems to contradict the experimental results, as the switch from the C^2-C^7 to the C^2-C^6 cyclization is experimentally well documented with *t*Bu groups.[11] The geometries of the transition states of the reactions of **3** rationalize this behavior on the basis of differential steric effects. In line with strong steric interactions in the C^2-C^7 cyclization, the allene unit is increasingly bent in the transition state from 144° (**1**) to 141° (**2**) to 134° (**3**). Similarly, the bending of the alkyne terminus is increased from 147° (**1**) to 143° (**2**) to 134° (**3**). This shows that both terminal groups repel each other for R = *t*Bu.

In contrast, the geometrical parameters of the transition state of the C^2-C^6 cyclization clearly indicate that the steric interactions are weaker than in the C^2-C^7 cyclization. Therefore, on the basis of the smaller distance between the repelling alkyne and allene substituents in the C^2-C^7 cyclization than in the C^2-C^6 cyclization, the introduction of bulky substituents at the allene terminus is expected to raise the activation energy of the C^2-C^7 cyclization above that of the C^2-C^6 cyclization. Our findings agree with new results of Gillmann et al., who showed that the switch from the C^2-C^7 cyclization to the C^2-C^6 cyclization takes place only if both the alkyne and the allene terminus possess bulky substituents.[12] Electronic effects, as discussed for R = Ph, also seem to increase the barrier to the C^2-C^7 cyclization. This can be seen from the bond between the alkyne group and the substituent (*t*Bu), which is elongated by about 0.04 Å on going from the reactant to the transition state of the C^2-C^7 cyclization.

The reaction energies (ΔE_r) have been calculated for both cyclization pathways of **1** and **2**.[13] Notably, for both substituents at the alkyne terminus the C^2-C^7 cyclization is favored thermodynamically over the C^2-C^6 cyclization, which indicates that the switch from the C^2-C^7 cyclization to the C^2-C^6 cyclization is kinetically controlled.



Scheme 3. The intermediates in the C^2-C^6 (left) and C^2-C^7 cyclization (right) of **4**.

To test the influence of increasing mesomeric interaction on the activation energy, the cyclization of **4** ($R=NH_2$) was investigated. Interestingly, the activation energy for the C^2-C^6 cyclization is reduced by about 17 kcal mol^{-1}, while the activation energy of the C^2-C^7 cyclization is only lowered about 1 kcal mol^{-1}. In addition, both cyclizations become strongly exothermic, with $\Delta E_r = -37$ kcal mol^{-1} for the C^2-C^6 cyclization and -34 kcal mol^{-1} for the C^2-C^7 cyclization. The reasons for the drastic changes are outlined in Scheme 3 and Figure 1b, c. Because of the influence of the substituent NH_2, the product of the C^2-C^6 cyclization no longer is a biradical, but a carbene in which the C^2-C^7-N plane is rotated by about 40° toward the fulvene plane. The planarity at the NH_2 group is indicative of strong mesomeric interactions between the lone pair of the NH_2 group and the p orbital localized at the C^7 center, which lies perpendicular to the doubly occupied orbital at the same center (a″ symmetry). In contrast, the intermediate of the C^2-C^7 cyclization is still a biradical. The change in the value of ΔE_r for the C^2-C^7 cyclization results from mesomeric interactions between the NH_2 group and the benzene ring.

Our study rationalizes the switch between the two biradical cyclizations on the basis of mainly steric (R = *t*Bu) or electronic effects (R = Ph). Moreover, the results for R = NH_2 predict that the activation energy of the C^2-C^6 cyclization can be reduced even further. However, a change in the reaction mechanism is found. An experimental verification of this prediction is currently being undertaken.

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[9] A correct description of biradical intermediates needs a multireference configuration interaction (MR-CI) approach. However, because the biradical nature of the wavefunction develops after the transition state—that is, in the density functional theory (DFT) calculations $<S^2>=0$ was found for all transition states (B. Engels, M. Hanrath, *J. Am. Chem. Soc.*, in press)—the influence of substituents on the activation energy of both processes can be obtained from less demanding DFT calculations. Consequently, in the present work the influence of the substituents at the alkyne terminus on the activation energy of both cyclizations was studied with the density functional approach in combination with a 6-31G* AO basis set, while an individually selecting MR-CI approach in combination with a DZP basis set (T. H. Dunning Jr., *J. Chem. Phys.* **1970**, *53*, 2823) was used for the computation of the reaction energies (ΔE_r). The reference space of the individually selecting MR-CI computations consisted of up to 15 configurations, leading to total MR-CI configuration spaces of more than 500×10^6 configuration state functions (CSFs). The secular equations actually solved were in the order of 4×10^6 CSFs. The influence of the neglected CSFs was estimated by the Buenker–Peyerimhoff extrapolation (R. J. Buenker, S. D. Peyerimhoff, *Theor. Chim. Acta* **1975**, *39*, 217; R. J. Buenker, S. D. Peyerimhoff, W. Butscher, *Mol. Phys.* **1978**, *35*, 771; R. J. Buenker, R. A. Phillips, *J. Mol. Struct. THEOCHEM* **1985**, *123*, 291, and references therein). The influence of higher excitations are estimated by the normalized form of the Davidson correction (J. E. Del Bene, E. A. Stahlberg, I. Shaviatt, *Int. J. Quantum. Chem. Symp.* **1990**, *24*, 455). In these calculations, abbreviated in the following as MR-CI + Q, all valence electrons were correlated. The calculations were performed with the DIESEL-MR-CI program package (B. Engels, M. Hanrath, DIESEL-MR-CI (*d*irect *i*nternal *e*xternal separated individually *sel*ecting MR-CI) program package, Universität Bonn, Germany, **1997**; M. Hanrath, B. Engels, *Chem. Phys.* **1997**, *225*, 197). The transition states were optimized and characterized by frequency calculations. As discussed above, the DFT (B33LYP) approach was used (A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648; C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785). These calculations were performed with the Gaussian 94 program package (M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez, J. A. Pople, Gaussian, Inc., Pittsburgh PA, **1995**) and the TurboMol program package (R. Ahlrichs, M. Baer, M. Haeser, H. Horn, C. Koelmel, *Chem. Phys. Lett.* **1989,** *162*, 165; O. Treutler, R. Ahlrichs, *J. Chem. Phys.* **1995**, *102*, 346).
[10] Experimental studies[7] provided an activation energy of 24–25 kcal mol^{-1} for the C^2-C^6 cyclization for R = Ph, R^1 = *n*Bu, R^2 = $POPh_2$ (Scheme 1), while for R = H, R^1 = *n*Bu, R^2 = $POPh_2$ an activation energy of about 22 kcal mol^{-1} was measured for the C^2-C^7 cyclization. Test calculations for R = H showed that the $POPh_2$ group lowers the barrier by about 3–4 kcal mol^{-1}.
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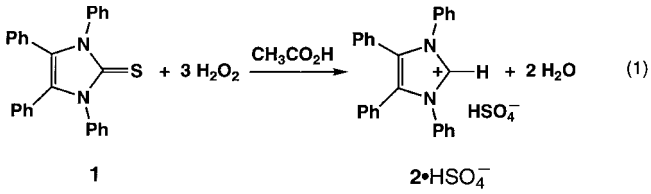
[13] Our calculations for R = H and R = Ph identify both biradical intermediates as minimum structures on the potential surface. A zwitterionic mechanism could be ruled out, because the first excited singlet state of the biradical intermediate, which has a zwitterionic structure, lies above the singlet ground state.

1,3,4,5-Tetraphenylimidazol-2-ylidene: The Realization of Wanzlick's Dream**

Anthony J. Arduengo III,* Jens R. Goerlich, Roland Krafczyk, and William J. Marshall

In 1970 H.-J. Schönherr and H.-W. Wanzlick postulated the formation of the title compound **3** upon deprotonation of the corresponding imidazolium perchlorate $\mathbf{2}\cdot ClO_4^-$ with potassium *tert*-butoxide.[1] However, carbene **3** was neither observed nor isolated, but rather allowed to react in situ with water in the presence of oxygen from the air. The resulting ketone, 1,3,4,5-tetraphenylimidazol-2-one, was characterized as the secondary reaction product. The apparent absence of any attempt to isolate the putative carbene **3** or its dimer may have been a result of the then prevalent idea that such imidazol-2-ylidenes really exist as the corresponding dimers (olefins)[2] or are at best highly labile intermediates.[3] Nonetheless, for steric and energetic reasons, Wanzlick postulated the presence of the carbene **3**.

We now report the synthesis, characterization, and X-ray crystallographic structure determination of **3.** A modification of the procedure published by Wanzlick makes it possible to isolate the carbene.[1] The imidazolium salt $\mathbf{2}\cdot HSO_4^-$ was obtained by oxidation of 1,3,4,5-tetraphenylimidazol-2-thione (**1**)[4] with a solution of 30% aqueous hydrogen peroxide in acetic acid [Eq. (1)].[1] The amount of hydrogen peroxide



(1)

specified in Wanzlick's procedure for the preparation of this salt is insufficient to form the hydrogensulfate quantitatively. Three moles of hydrogen peroxide are required per mole of thione because sulfur remains in the product in the form of a hydrogensulfate counterion; it is not lost as sulfur dioxide as assumed by Wanzlick et al. Wanzlick and co-workers also reported conversion of the initially formed imidazolium salt into a perchlorate, which was in turn used in their attempts to generate the carbene. It is possible that traces of the hydrogensulfate anion (similar in size and molecular weight to perchlorate) contaminated their imidazolium perchlorate and

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