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On the Regioselectivity of the Cyclization of Enyne−Ketenes: A Computational Investigation and Comparison with the Myers-Saito and Schmittel Reaction

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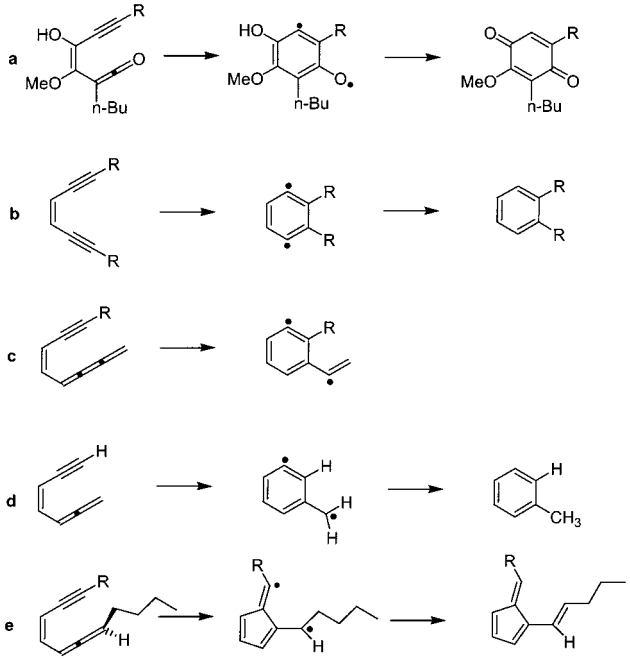
Abstract: The Moore (C^2-C^7) cyclization and the alternative C^2-C^6 cyclization of enyne−ketenes belong to the family of biradical cyclization reactions such as the Bergman reaction of ene−diynes, both the cyclizations of enyne−allenes and enyne−cumulenes. The latter garnered substantial interest due to their antitumor efficacy. The mechanisms of both cyclization modes of enyne−ketenes are still unclear, but as the enyne−ketenes can formally be regarded as heteroanalogues of enyne−allenes, both cyclizations are expected to react via biradical routes. Nevertheless, as shown recently for cyclic allenes, the substitution of a methylene group by oxygen can lead to different energetic ordering of the electronic states of the key intermediates. To elucidate the mechanism, the present work investigates the course of both cyclization modes for various model compounds. To reveal general motifs for the large family of biradical cyclizations, a comparison with enyne−allenes is performed.

1. Introduction

The Moore cyclization of enyne−ketenes[1−5] yielding quinones via phenoxy biradicals (see a in Scheme 1) belongs to the family of biradical cyclization reactions such as the Bergman reaction of ene−diynes (b),[6,7] the cyclization of enyne−cumulenes (c),[8] and the Myers-Saito reaction of enyne−allenes (d),[9,10] together with its regioalternative Schmittel cyclization (e).[11−14]

The Bergman and the Myers-Saito reactions were awarded with substantial interest, because they represent the basis of the antitumor antibiotic efficacy of ene−diynes and enyne−allenes. Despite its DNA strand cleavage ability, the Moore cyclization did not gained as much attention as the formerly mentioned Bergman or Myers-Saito cyclizations.

Scheme 1. Moore, Bergman, Myers, Myers-Saito, and Schmittel Cyclization of Enyne−Ketenes, Ene−Diynes, Enyne−Cumulenes, and Enyne−Allenes



As indicated in Scheme 2, the cyclization of enyne−ketenes possesses two reaction modes.[1] The first mode is the so-called Moore reaction (Scheme 2, lower pathway). It forms the new bond between C^2 and C^7. For this reaction pathway, several intermediates have to be considered. In addition to the biradical route leading to the intermediate **1c**, the reaction could also yield the cyclic allene **1d** or a zwitterionic intermediate **1e.** In addition to the C^2-C^7 cyclization, a five-membered ring between C^2

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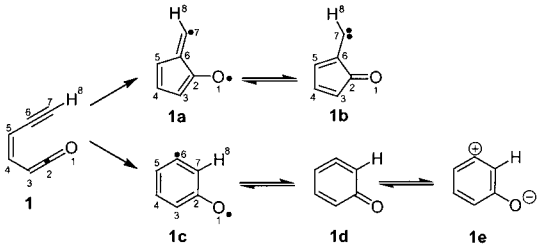
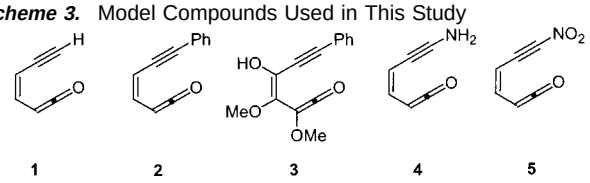
Scheme 2. Possible Reaction Routes for **1** and Biradical (**1a**, **1c**), Carbenelike (**1b**), and Allenic Intermediates (**1d**). The Zwitterionic Species (**1e**) Represents the Transition State for the Inversion of the Allene



Scheme 3. Model Compounds Used in This Study



and C^6 (Scheme 2, upper path) can be formed via the biradical pathway, yielding the σ,π-biradical **1a**, or via a carbenelike intermediate **1b**.

The mechanisms of both cyclization modes of the enyne−ketenes are unclear, but as the Moore cyclization of enyne−ketenes can be regarded as a heteroanalogue Myers-Saito reaction of enyne−allenes, both the six- and the five-membered ring cyclizations are expected to react via a biradical route. However, the differences in the electronic structure of the enyne−allenes and enyne−ketenes could lead to an energetic preference of the other intermediates. Such a preference was recently seen for cyclic allenes, where substitution effects reversed the energetic ordering of the biradical and zwitterionic species.[15,16]

To answer these questions, the present work investigates the course of both cyclization modes for the model compounds depicted in Scheme 3. For this instance, all stationary points of both reaction paths were computed and characterized. To study whether a general motif exists for the family of reactions discussed above, relations between enyne−ketenes and enyne−allenes compounds are also investigated.

2. Computational Aspects

Geometrical parameters of all stationary points were optimized employing analytic energy gradients within the Density Functional Theory (DFT) framework as implemented in *Gaussian 98*.[17] For the DFT calculations, the BLYP and B3LYP[18,19] functional in connection with a 6-31G(d), 6-311G(d),[20] and a *cc*-pVDZ[21] basis set was employed using a spin and space unrestricted ansatz. All stationary points were analyzed by computed harmonic frequencies on the same level of theory and tested for wave function instabilities.[22,23] Vibrational, thermal, and entropy corrections at 298 K were computed on the B3LYP/6-31G(d) level of theory.

Transition state energies for **1** were also obtained by single point computations employing the more reliable closed shell Coupled Cluster (CCSD and CCSD(T)) ansatz[24−26] in conjunction with a *cc*-pVDZ basis set to evaluate the quality of the DFT calculations. These computations were performed with the MOLPRO 2000.1 package.[27] The reliability of the Coupled Cluster ansatz was validated using the T_1 diagnostics.

Reaction energies for **1** have been computed using a multireference configuration interaction ansatz in connection with a Davidson estimate of quadruple excitations (MR−CI+Q) as implemented in the DIESEL-MRCI package,[28] as well as the CASPT2 implementation of the MOLCAS program package.[29] These computations based on CASSCF(10,10) wave functions employing a *cc*-pVDZ basis set and Widmarks *ano-l* basis set[30] in a (8s4p) → [3s1p] contraction for hydrogen and a (14s9p4d) → [4s3p2d] contraction for carbon and oxygen. The contraction schemes were taken from the basis set library of the MOLCAS program package. This basis set will be denoted as VTZP. The reference space of the individually selecting MR−CI consisted of up to 15 configuration state functions (CSF) generating a configuration space of up to 10^8 CSF. The secular equations to solve were up to the order of 10^7.

3. Investigation of the Parent System

The cyclization of enyne−ketenes in principle possesses two possible regioalternatives. One mode of cyclization is a formation of a five-membered ring between C^2 and C^6 (see Scheme 2, upper path) on a biradical pathway yielding the σ,π-biradical **1a** or the carbenelike species **1b**. The second mode, known as the Moore reaction, forms the new bond between C^2 and C^7 (Scheme 2, lower pathway). Possible intermediates for this reaction mode are the biradical (**1c**), the cyclic allene (**1d**), and the zwitterion (**1e**). Various computational studies prove DFT to be in principle appropriate to treat reactions including biradical intermediates.[31−34] This finding is helpful since mul-

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Table 1. Computed Barriers of Activation for Model System **1**[a]

	C^2–C^6 cyclization			C^2–C^7 cyclization		
method	$\Delta E^{\ddagger}$	$\Delta H^{\ddagger}_{298}$	$\Delta G^{\ddagger}_{298}$	$\Delta E^{\ddagger}$	$\Delta H^{\ddagger}_{298}$	$\Delta G^{\ddagger}_{298}$
B3LYP/6-31G(d)	+41.2	+39.4	+41.4	+13.3	+12.1	+13.6
B3LYP/6-311G(d)	+45.6	+43.7	+45.8	+16.7	+15.6	+17.8
BLYP/6-31G(d)	+30.6	+29.1	+31.1	+9.6	+8.7	+10.5
CCSD/cc-pVDZ//B3LYP/6-31G(d)[b]	+48.0			+23.7		
CCSD/cc-pVDZ//BLYP/6-31G(d)[b]	+45.5			+22.4		
CCSD(T)/cc-pVDZ//B3LYP/6-31G(d)[b]	+41.3			+17.6		
CCSD(T)/cc-pVDZ//BLYP/6-31G(d)[b]	+36.2			+16.9		

[a] All energies are given in kilocalorie/mole. [b] CCSD and CCSD(T) calculations employing larger basis sets could not be performed due to computational limitations.

Table 2. Selected Geometrical Parameters for **1** and the TS for the C^2–C^6 Cyclization[a]

	1		TS C^2–C^6 cyclization	
parameter	B3LYP	BLYP	B3LYP	BLYP
$d(C^2-C^6)$	3.01	3.04	1.69	1.76
$d(O^1-C^2)$	1.17	1.18	1.20	1.21
$d(C^6-C^7)$	1.21	1.23	1.31	1.29
$\angle(O^1-C^2-C^3)$	174	174	121	124
$\angle(C^6-C^7-H^8)$	179	179	133	142

[a] Distances are given in angstroms and angles in degrees.

tireference methods for open shell and Coupled Cluster calculations for closed shell species are only applicable to smaller systems, leaving the computationally less demanding DFT to be the only opportunity to treat systems including all substituents present in the experimentally handled compound. Nevertheless, the results of these computational studies show that a validation of the DFT approach is necessary because various pitfalls are known for systems with complicated electronic structure. Additionally, it cannot be predicted which functional gives the most accurate values for a given class of compounds. For the cyclization of the parent system **1**, such a validation can be taken from Tables 1−3. Table 1 shows the computed activation energies for the reaction routes from **1** to **1a** (C^2-C^6 cyclization) and to **1c**−**e** (C^2-C^7 cyclization). The computed geometrical parameters can be taken from Table 2. Table 3 contains the reaction energies.

The transition states (TS) of the C^2-C^6 cyclization to **1a** and of the C^2-C^7 cyclization to **1c** possess almost complete closed-shell character with only minor spin contamination which allows the use of CCSD and CCSD(T) as more reliable methods to test the B3LYP and BLYP functionals. The activation energy for the C^2-C^6 cyclization using B3LYP/6-31G(d) is predicted to be 41.2 kcal/mol with a slight thermodynamic correction to the Gibbs free energy of 41.4 kcal/mol. It agrees perfectly with the CCSD(T) energy based on the same geometry (41.3 kcal/mol). With respect to CCSD(T), B3LYP/6-31G(d) underestimates the barrier height of the alternative reaction (C^2-C^7 cyclization) by about 4 kcal/mol (13.3 kcal/mol vs 17.6 kcal/mol). Corrections to the Gibbs free energy do not change the barrier of activation significantly ($\Delta G^{\ddagger}_{298} = 13.6$ kcal/mol compared to $\Delta E^{\ddagger} = 13.3$ kcal/mol). CCSD yields the same qualitative picture as CCSD(T) but predicts slightly increased barriers of activation for both the C^2-C^6 and the C^2-C^7 cyclizations. The BLYP functional seems not to be appropriate to describe the reaction modes. The computed barriers are much lower than the CCSD(T) counterparts (30.6 vs 41.2 kcal/mol). Additionally, the computed geometries point to much more productlike transition states (Table 2).

Due to the strong change in the electronic structure along the reaction path, the computation of the reaction energies (**1** → **1a**, **1** → **1c**−**e**) is quite demanding. For the C^2-C^6 cyclization (**1** → **1a**), B3LYP/cc-pVDZ predicts the reaction energy to be 25 kcal/mol. This value lies between the values obtained with CASPT2/cc-pVDZ (23 kcal/mol) and MRCI+Q/cc-pVDZ (27 kcal/mol), underlining again the applicability of the B3LYP functional in the present context. Improving the basis set from VDZ to VTZ leads to only small changes in the computed reaction energies if the CASPT2 or the MRCI+Q approach is employed. Interestingly, the DFT approach possesses a stronger basis set dependency than the more sophisticated approaches.

Similar to the enyne−allenes,[35] the biradical **1c** and the allene structure **1d** of the C^2-C^7 cyclization are found to be very close in energy, whereas the zwitterionic structure **1e** lies much higher. The most reliable values are presumably given by the MRCI+Q approach in combination with the VTZP basis set. While the difference between **1c** and **1d** is computed to be 5−6 kcal/mol, the energy difference between **1c** and **1e** is about 16 kcal/mol. While the B3LYP functional agrees nicely with the more sophisticated approaches, the BLYP functional again deviates by computing **1d** to represent the lowest lying intermediate of the C^2-C^7 cyclization. Summarizing our evaluation, in the present system, B3LYP is applicable to locate accurate transition structures and reaction energies. As found in other examples, BLYP seems to be inadequate. As expected, the CASSCF and the MP2 approaches lead to completely wrong results.

Our computations show that for the parent system **1** the Moore reaction (C^2-C^7 cyclization) is kinetically and thermodynamically strongly favored with respect to the C^2-C^6 cyclization. In comparison to *Z*-1,2,4-heptatriene-6-yne which represents the parent system of enyne−allenes, **1** possesses a much higher barrier for the C^2-C^6 cyclization (41 vs 31 kcal/mol) while the barrier for the C^2-C^7 cyclization is reduced (13.3 vs 24.0 kcal/mol). This behavior may arise from a diminished electron density in the enyne−ketene compared to the enyne−allene which favors the C^2-C^7 cyclization and stipulates the C^2-C^6 cyclization. Both enyne−ketene cyclizations are more endothermic by about 10 kcal/mol than their counterparts in the enyne−allenes. While $\Delta_R G_{298}$ of the C^2-C^6 cyclization is +27 kcal/mol for the enyne−ketene **1a**, a value of about +13 kcal/mol[36] is found for the enyne−allenes. For the C^2-C^7

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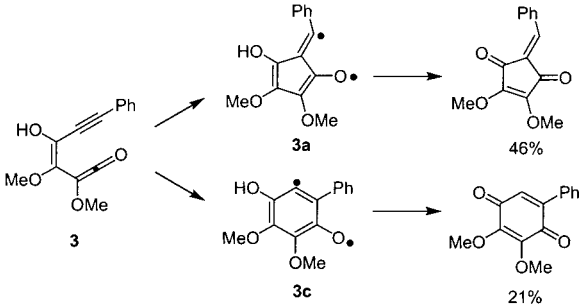
Table 3. Computed Reaction Energies for Model System **1**[a]

	 **1a**			 **1c**			 **1d**			 **1e**		
Method	$\Delta_R E$	$\Delta_R H_{298}$	$\Delta_R G_{298}$	$\Delta_R E$	$\Delta_R H_{298}$	$\Delta_R G_{298}$	$\Delta_R E$	$\Delta_R H_{298}$	$\Delta_R G_{298}$	$\Delta_R E$	$\Delta_R H_{298}$	$\Delta_R G_{298}$
B3LYP/6-31G(d)	+23.4	+22.8	+24.8	+2.0	+2.2	+4.8	+6.8	+7.2	+9.6			
B3LYP/6-311G(d)	+28.8	+28.1	+30.2	+7.9	+8.1	+10.7	+11.5	+11.8	+14.2			
BLYP/6-31G(d)	+27.1	+26.4	+28.5	+6.3	+5.8	+8.9	+4.7	+4.9	+7.4			
B3LYP/cc-pVDZ	+25.0	+24.2	+26.3	+5.4	+5.6	+8.1	+9.8	+10.0	+12.4	+13.4	+12.1	+14.6
B3LYP/cc-pVTZ//B3LYP/cc-pVDZ	+29.4			+8.8			+11.8			+16.1		
MP2/cc-pVTZ//B3LYP/cc-pVDZ [(a)]	+61.1			+33.0			+12.0			+19.5		
CASSCF(10,10)/cc-pVDZ//B3LYP/cc-pVDZ	+33.2			+11.6			-4.2			+38.4		
CASPT2/cc-pVDZ//B3LYP/cc-pVDZ	+22.8			+1.0			+7.8			+9.8		
MRCI+Q/cc-pVDZ//B3LYP/cc-pVDZ	+26.6			+4.1			+9.8			+18.0		
CASSCF(10,10)/VTZP//B3LYP/cc-pVDZ	+24.3			+2.1			-15.0			+27.7		
CASPT2/VTZP//B3LYP/cc-pVDZ	+23.7			+1.5			+7.8			+9.0		
MRCI+Q/VTZP//B3LYP/cc-pVDZ	+26.0			+3.0			+7.7			+15.9		

Geometries for **1a** and **1c** were calculated in C_1 symmetry for the 6-31G(d) and 6-311G(d) and in C_s symmetry for the cc-pVDZ basis set. **1d** was computed in C_1 symmetry for all basis sets used. The transition state **1e** for the inversion of the cyclic allene **1d** could only be located in C_s symmetry. [(a)] Reactant and closed-shell species **1d** and **1e** were calculated using spin restricted MP2 while for biradicals **1a** and **1c** spin unrestricted UMP2 was applied. Spin projected MP2 (PMP2) worsens the results dramatically.

[a] All energies are given in kilocalorie/mole.

Scheme 4. Experimental Regioselectivity of **3**



cyclization, the corresponding numbers are about +6 and −11 kcal/mol, respectively.[37]

4. Influence of the Substituents

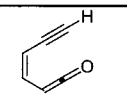
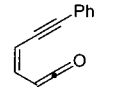
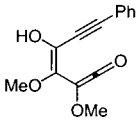
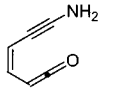
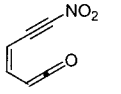
From the structural similarity between enyne−allenes and enyne−ketenes, a comparable reaction scope can be expected. Indeed, although **1** reacts in a C^2-C^7 cyclization leading to 1,4-benzoquinone, for the phenyl-substituted enyne−ketene **3** (see also Scheme 4), Moore and co-workers found that the product of the competing five-membered C^2-C^6 cyclization represents the major product (46% yield vs 21%).[5] This regioselectivity resembles the regioselectivity found for the enyne−allenes systems[36] but is less pronounced. For an understanding of the differences and the similarities, we computed the reaction barrier for various model compounds (Table 4). If the hydrogen of the enyne terminus in the parent compound **1** is replaced by a phenyl (**2**), the activation barrier for the C^2-C^6 cyclization ($\Delta G^{\ddagger}_{298}$ = 28.7 kcal/mol) decreases by about 13 kcal/mol compared to the parent system **1** ($\Delta G^{\ddagger}_{298}$ = 41.4 kcal/mol). This reduction of the free energy of activation for the C^2-C^6 cyclization of **2** is more pronounced than in the enyne−allene compound for which Ph substitution diminished $\Delta G^{\ddagger}_{298}$ only from 31.4 to 28.7 kcal/mol. The increase of the reaction barrier for the C^2-C^7 cyclization of **2** by about 6 kcal/mol (13.6 kcal/mol (**1**) vs 19.8 kcal/mol (**2**)) is of the same order of magnitude as was computed for the corresponding enyne−allenes ($\Delta G^{\ddagger}_{298}$ = 24.0 kcal/mol to 29.8 kcal/mol). Although the influence of the phenyl group is considerable larger for the enyne−ketenes than for the enyne−allenes, **2** prefers the Moore reaction by about 10 kcal/mol over the C^2-C^6 cyclization. This prediction also holds if we consider that the B3LYP approach seems to underestimate the barrier of the C^2-C^7 cyclization by about 4 kcal/mol while the barrier of the C^2-C^6 cyclization seems to be predicted in a better accord with higher level CCSD(T) computations.

The switch from the C^2-C^7 to the C^2-C^6 cyclization is found if the OH and OMe substituents being present in the experimentally studied compound are taken into account (**3**). These oxygen-containing substituents further decrease the free energy of activation for the C^2-C^6 cyclization from $\Delta G^{\ddagger}_{298}$ = 28.7 kcal/mol (**2**) to $\Delta G^{\ddagger}_{298}$ = 18.7 kcal/mol (**3**) while $\Delta G^{\ddagger}_{298}$ for the C^2-C^7 cyclization raises slightly from 19.8 kcal/mol (**2**) to 21.9 kcal/mol (**3**), leading to a preference of the C^2-C^6 cyclization and explaining the experimentally found regioselectivity.

The influence of the phenyl group on the reaction barriers of both cyclization modes is much stronger than that found in the enyne−allenes but is not sufficient to induce the shift from the C^2-C^7 cyclization to the C^2-C^6 cyclization. As already mentioned above, this difference from the enyne−allene systems is a consequence of the much higher C^2-C^6 cyclization barrier

(37) MRCI+Q calculations employing a cc-pVTZ basis set neglecting the set of f-functions on carbon.[15]

Table 4. Activation Energies for Substituted Enyne–Ketenes **1**–**5** Computed at the B3LYP/6-31G(d) Level of Theory[a]

	System	C^2-C^6 cyclization			C^2-C^7 cyclization		
		$\Delta E^{\neq}$	$\Delta H^{\neq}_{298}$	$\Delta G^{\neq}_{298}$	$\Delta E^{\neq}$	$\Delta H^{\neq}_{298}$	$\Delta G^{\neq}_{298}$
1		+41.2	+39.4	+41.4	+13.3	+12.1	+13.6
2		+28.1	+26.4	+28.7	+18.8	+17.3	+19.8
3		+18.9	+17.4	+18.7	+20.7	+19.2	+21.9
4		+8.8	+7.6	+10.2	+11.4	+10.4	+13.5
5		+27.8	+25.8	+27.4	+16.9	+15.4	+17.5

[a] All energies are given in kilocalorie/mole.

found for the parent system **1** which in turn may result from the presumably diminished electron density in enyne–ketene. The shift from C^2–C^7 to C^2–C^6 cyclization takes place if the lower electron density is compensated by the additional donor groups OH and OMe which reduce the barrier of the C^2–C^6 cyclization and increase the barrier of the C^2–C^7 cyclization. This is in line with the finding of Brunette and Lipton[38] that oxyanion substitution significantly accelerates the C^2–C^6 cyclization in enyne–allenes.

To investigate similarities and differences between enyne–allenes and enyne–ketenes in more detail, we also studied the influence of strong electron-donating substituents (NH_2 in **4**) and of electron-withdrawing substituents (NO_2 in **5**). For enyne–allenes both substituents preferred the C^2–C^6 cyclization but possessed a carbenelike instead of a biradical intermediate.[16,36]

Compared to the parent compound **1** ($\Delta G^{\ddagger}_{298}$ = 41.4 kcal/mol), the amino-substituted enyne–ketene **4** possesses a dramatically lower free energy of activation ($\Delta G^{\ddagger}_{298}$ = 10.2 kcal/mol) for the C^2–C^6 cyclization. In contrast, the activation barrier for the C^2–C^7 cyclization remains almost constant at about 13.5 kcal/mol. In agreement to the enyne–allene analogue the NH_2 substituent leads to a preference of the C^2–C^6 cyclization but for the enyne–allene the activation barriers were found to be significantly higher ($\Delta G^{\ddagger}_{298}$ = 17.8 kcal/mol for the C^2–C^6 cyclization and $\Delta G^{\ddagger}_{298}$ = 22.7 kcal/mol for the C^2–C^7 cyclization).[36] If the electron-donating amino group is replaced by the strong electron-withdrawing nitro substituent the activation barrier for the C^2–C^6 cyclization decreases from 41.4 kcal/mol (**1**) to 27.4 kcal/mol (**5**). This change is insufficient to switch the regioselectivity of the reaction as the increase in the free energy of activation $\Delta G^{\ddagger}_{298}$ for the C^2–C^7 cyclization by about 3–4 kcal/mol to +17.5 kcal/mol (**5**) is too low.

Both the electron-donating NH_2 and the electron-withdrawing NO_2 lower the activation barriers and lead to carbenelike intermediates for the C^2–C^6 cyclization, i.e., change the reaction mechanism. The reaction energies are given in Table 5. While **1a** was shown to represent a σ,π-biradical, for **4** a carbenelike intermediate is found which possesses a lone-pair σ-orbital centered at the carbon atom in α-position to the NH_2 substituent. Figure 1 sketches the results obtained from an NBO analysis.[39] The preference for the carbene structure over the biradical can be explained by π-conjugation due to the planar NH_2-substituent. This interaction lowers the π-orbital and leads to doubly occupied σ and π orbitals (see Figure 1). Consequently, in contrast to **1**–**3**, the C^2–C^6 cyclization of **4** has to be looked upon as a carbenelike reaction mechanism. In contrast, the main intermediate for the Moore type reaction still remains a biradical. It is predicted to lie below the cyclic allene by about 9.0 kcal/mol.

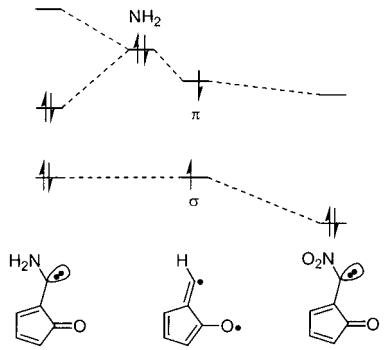


Figure 1. Orbital scheme for the effect of electron-donating and -withdrawing substituents on biradicals.

Also, the C^2–C^6 intermediate of **5** possesses a carbenelike electronic structure; the reasons are different, however. As indicated by NBO analyses (Figure 1), the substituent NO_2 lowers the σ-orbital by its strong electron-withdrawing effect. As a consequence, the energetic difference between the σ- and π-orbital is enlarged, leading to a double occupancy of the σ-orbital. Similar effects were also found for the enyne–allene.[16]

(38) Brunette, S. R.; Lipton, M. A. *J. Org. Chem.* **2000**, *65*, 5114–5119.

(39) Glendering, E. D.; Reed, A. E.; Carpenter, J. E.; Weinhold, F. *NBO*, ver. 3.1; Pittsburgh, PA, Gaussian. Inc, 1998.

5. Summary

In the present work, the Moore (C^2-C^7) cyclization and its regioalternative C^2-C^6 cyclization are investigated. While the parent system **1** is studied with high-level ab initio methods (MR−CI+Q, CASPT2, CCSD(T)), substituent effects are included, employing the DFT approach. To study similarities to other biradical cyclization reactions, the present results are compared to biradical cyclizations of enyne−allenes.

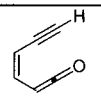
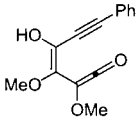
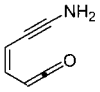
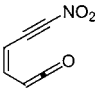
For the parent system **1**, the C^2-C^7 cyclization is kinetically and thermodynamically strongly favored with respect to the C^2-C^6 cyclization ($\Delta G^{\ddagger}_{298} = 41$ kcal/mol vs $\Delta G^{\ddagger}_{298} = 18$ kcal/mol and $\Delta_R G_{298} = +3$ kcal/mol vs $\Delta_R G_{298} = +26$ kcal/mol). The C^2-C^7 cyclization proceeds via the biradical intermediate **1c** which is computed to be 5 kcal/mol more stable than the cyclic allene **1d** and 13 kcal/mol lower in energy than the zwitterionic state **1e**.

The main difference between **1** and the parent system of the enyne−allenes (*Z*-1,2,4-heptatriene-6-yne) is the barrier to the C^2-C^6 cyclization (41 kcal/mol for **1**, 31 kcal/mol for *Z*-1,2,4-heptatriene-6-yne). Furthermore, both possible cyclization modes for the enyne−ketene are more endothermic than those for the enyne−allene. Both may originate from the diminished electron density in the enyne−ketene compared to the enyne−allene which seems to favor the C^2-C^7 cyclization and disfavors the C^2-C^6 cyclization.

Substituent effects are more pronounced for the enyne−ketenes than for the enyne−allenes. For example, the reaction barrier for the C^2-C^6 cyclization decreases by 13 kcal/mol if the hydrogen of the alkyne terminus is substituted by a phenyl group. For the enyne−allene, the barrier decreases by only 3 kcal/mol. However, due to the strong difference found for the parent system **1**, the shift from the C^2-C^7 to the C^2-C^6 cyclization only takes place if additional OH and OMe substituents (**3**) are present.

Our findings about the influence of strong electron-donating or -withdrawing substituents underline the strong similarities between enyne−ketenes and enyne−allenes (see Figure 1). Both NH_2 (**4**) and NO_2 (**5**) at the alkyne terminus lead to carbenelike intermediates instead of biradicals, but the reasons are different, however.

Table 5. $\Delta_R G_{298}$ for Intermediates Representing Local Minima of Enyne−Ketenes **1**−**5** Computed at the B3LYP/6-31G(d) Level of Theory[a]

System		Intermediate			
		a	**b**	**c**	**d**
1		+24.8		+4.8	+9.6
2		+17.7		+9.6	+15.0
3		+0.5		-4.2	+2.7
4			+5.8	-4.5	+4.4
5			+18.4	+3.5	+7.2

[a] All energies are given in kilocalorie/mole, and **a**−**d** correspond to the various intermediates as denoted in Scheme 2.

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Supporting Information Available: Absolute energies and computed structures of all stationary points for **1**−**5** in Cartesian coordinates (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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