THERMAL REARRANGEMENTS OF HETEROATOM-BRIDGED POLYUNSATURATED HYDROCARBONS

by

BINH H. BUI

(Under the Direction of Peter R. Schreiner)

ABSTRACT

In predicting new reactions, systematic strategies involving the classification of systems of interest and methodological applications of computational tools are used to study heterosubstituted polyunsaturated hydrocarbons. Although this is a rather "heuristic approach," it provides qualitatively reasonable results and collective findings of reaction families. A systematic application of the BLYP/6-311+G*//BLYP/6-31G* computational scheme was utilized to study the thermal rearrangements of 4-heteroatom-1,2-hexadiene-5-ynes (Chapter 2), 3-heteroatom-pent-1-en-4-yn-1-ones (Chapter 3), and (hetero)atom-bridged diallenes (Chapter 4). It was found that the *aromatization* 2,6-cyclization path leading to the formally aromatic five-membered ring products are preferred and experimentally accessible. Protonation of the heteroatom **X** resulted in either the 1,6-Claisen-type rearrangement to form the stable acyclic product or the competitive 1,6-cyclization mode to form homoaromatic six-membered ring products. The σ-electron-withdrawing and π-electron-donating abilities of the heteroatom (or group) **X** have been determined to be effective in governing the reaction barriers ($\mathbf{TS_{26}}$) but not the reaction energies.

INDEX WORDS: enyne-allenes, enyne-ketenes, diallenes, enones, enynes, radicals, reaction family, heterosubstituted polyunsaturated hydrocarbons, rearrangements

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by

BINH H. BUI

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by

BINH H. BUI

Major Professor:	George Majetich
Committee:	Robert S. Phillips
	Timothy M. Dore

Electronic Version Approved:

Maureen Grasso
Dean of the Graduate School
The University of Georgia
August 2006

DEDICATION

To my Savior, the Lord Jesus Christ, who has enabled and instilled into me the Hope, Love and Boldness.

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CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

The discoveries of many natural antibiotics carrying the enediyne chemical warhead capable of destroying the DNA of bacteria and viruses have resulted in a new classification[1] of these compounds to focus the research on their chemical and biological properties. This opens the way for future development of clinically useful antitumor agents. Examples are several families of the chemotherapeutic enediyne class of antibiotics (Figure 1), such as Calicheamicin γ^{I}_{1} (**1**), Dynemicin (**3**), and Neocarzinostatin (**4**) that have been thoroughly studied for their unique structure characteristics, mode of actions, and antitumor activity. However, one of the challenges for studying these prodrugs is the theoretical description of the electronic structure of their biradical intermediates. These biradicals are characterized by singlet ground states[2-7] and small singlet–triplet separations (ΔE_{ST}). The theoretical description of singlet biradicals is difficult due to their inherent multireference character. In particular, spin or spatial symmetry breaking problems arise when using approximate wavefunction.[4-5, 8] Several theoretical methodologies [9-11] have been reviewed and applied for these biradicals. Quantum chemical calculations, such as the complete active space self-consistent field with perturbation methods (CASPT2),[12-14] the multireference configuration interaction (MRCI) methods,[15] and the Brueckner doubles (BD) ansatz[16] have become standard computational approaches for these multireference systems.

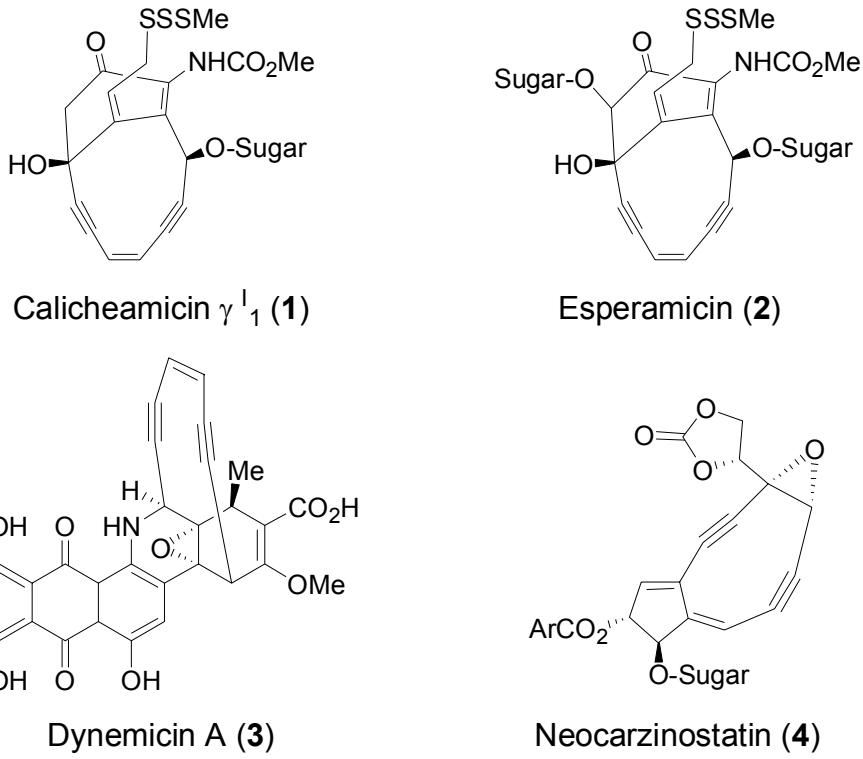
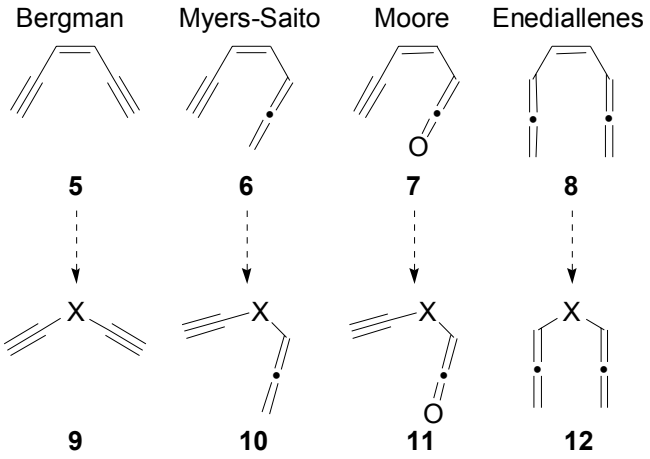


Figure 1. Structural formulas of the enediyne antibiotics

Another approach is DFT,[17] which has been utilized widely to investigate these multiconfigurational systems because of its computational efficacy. However, on the case-to-case basis the biradical system of interest must be examined carefully with respect to their multiconfigurational characters to select an appropriate method.[11, 18] Methodological applications of DFT have proven not only useful for studying biradical systems but enabled also collective findings or predictions[18] leading to systematic extensions of studies on similar reactions that involve multireference intermediates. Examples are our group's studies on polyunsaturated hydrocarbon systems.[18-22]

My graduate study of the heterosubstituted polyene and polyyne reaction systems (Scheme 1) not only enabled me to conduct research methodologically but to also learn different

ab initio programs and methods in order to elucidate chemical reaction mechanisms involved in gas-phase processes and statistical methods to understand the kinetics of those reactions.[23]



Scheme 1

My present studies are a continuing quest inspired by recent advancement of computation and information technologies that transform our understanding not only in surrounding physical worlds but also small biological systems. Furthermore, the same tools can be used to predict new chemical systems of the same reaction families. By completing my M.S. study, I look forward to applying my computational chemistry skills on combustion studies on chemical systems that are related to renewable energy.

Presented here are the three projects[22, 24-25] that systematically investigated the heteroatom effect on the action mode of several polyene and polyyne reactions (Scheme 1). The first project[24] focused on the cyclizations of the 4-heteroatom-1,2-hexa-diene-5-ynes (**10**). This type of reactions is an analogue to the enyne-allene (**6**) reactions, such as the Myers-Saito[26-27] and the Schmittel[28-29] cyclizations, of which the DNA-cleaving biradical intermediates are the focal point in antitumor drug chemistry. The heteroatom-substituted yne-

allenes (**10**), where the heteroatom substitutes the central olefinic bond of **6**, has been examined for its thermal rearrangements with respect to a selection of heteroatoms.

In the second project[25] various X-heteroatoms have been selected to study the rearrangements of 3-heteroatom-pent-1-en-4-yn-1-ones (**11**). Unlike the enyne-allene chemistry, which has received much attention for its potential drug application, the enyne-ketene (**7**) chemistry has attached little attention.[30-31] In addition, the chemistry of **11** has not been examined for its various cyclization modes and biradical natures of the respective intermediates. Hence, the heteroatom effect on the rearrangements of **11** was probed with respect to the criteria of its donating ability of lone pair electron to the π-electron molecular system.

The last project[22] is a study on the thermal rearrangements of the heteroatom-bridged diallenes (**12**). Although experimental data are available, our computational analyses provide not only validation of some experimental results, but also additional insights into the heteroatom effects on the ΔE_{ST} gap for the products. The choice of the heteroatom governs the reaction barriers and offers a tuning mechanism to control the ΔE_{ST} gap and total electronic spin of the formally aromatic five-membered products. All together the utilization of a systematic computational approach has resulted in comprehensive studies of the thermal rearrangements of the heteroatom-substituted polyunsaturated hydrocarbons.

1.1 REFERENCES

[1] Borders, D. B.; Doyle, T. W., Ed. (1995) *Enediyne Antibiotics as Antitumor Agents*. New York: Marcel Dekker.

[2] Marquardt, R.; Balster, A.; Sander, W.; Kraka, E.; Cremer, D.; Radziszewski, J. G., *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 955.

[3] Myers, A. G., *Tetrahedron Lett.* **1987**, *28*, 4493.

[4] Wenthold, P. G.; Squires, R. R.; Lineberger, W. C., *J. Am. Chem. Soc.* **1998**, *120*, 5279.

[5] Wenthold, P. G.; Wierschke, S. G.; Nash, J. J.; Squires, R. R., *J. Am. Chem. Soc.* **1993**, *115*, 12611.

[6] Logan, C. F.; Ma, J. C.; Chen, P., *J. Am. Chem. Soc.* **1994**, *116*, 2137.

[7] Roth, W. R.; Hopf, H.; Horn, C., *Chem. Ber.* **1994**, *127*, 1765.

[8] Perdew, J. P.; Savin, A.; Burke, K., *Phys. Rev. A: At. Mol. Opt. Phys.* **1995**, *51*, 4531.

[9] Borden, W. T., Ed. (1982) *Diradicals*. New York: Wiley.

[10] Michl, J.; Bonacic-Koutecky, V., *Tetrahedron* **1988**, *44*, 7559.

[11] Gräfenstein, J.; Cremer, D., *Phys. Chem. Chem. Phys.* **2000**, *2*, 2091.

[12] Andersson, K.; Malmqvist, P. A.; Roos, B. O., *J. Chem. Phys.* **1992**, *96*, 1218.

[13] Andersson, K., *Thermochim. Acta* **1995**, *91*, 31.

[14] Lindh, R.; Persson, B. J., *J. Am. Chem. Soc.* **1994**, *116*, 4963.

[15] Hanrath, M.; Engels, B., *Chem. Phys.* **1997**, *225*, 197.

[16] Handy, N. C.; Pople, J. A.; Head-Gordon, M.; Raghavachari, K.; Trucks, G. W., *Chem. Phys. Lett.* **1989**, *164*, 185.

[17] Gill, P. M. W., In *The Encyclopedia of Computational Chemistry*, (1998) Schleyer, P. v. R., Allinger, N. L., Clark, T, Gasteiger, J., Kollman, P.A., Schaefer, H. F., III, Schreiner, P. R., Eds., Chichester, U. K.: John Wiley & Sons; Vol. 1, p. 678.

[18] Schreiner, P. R.; Navarro-Vazquez, A.; Prall, M., *Acc. Chem. Res.* **2005**, *38*, 29.

[19] Prall, M.; Wittkopp, A.; Schreiner, P. R., *J. Phys. Chem. A* **2001**, *105*, 9265.

[20] Navarro-Vazquez, A.; Prall, M.; Schreiner, P. R., *Org. Lett.* **2004**, *6*, 2981.

[21] Kawatkar, S. P.; Schreiner, P. R., *Org. Lett.* **2002**, *4*, 3643.

[22] Bui, B. H.; Schreiner, P. R., *Eur. J. Org. Chem.* **2006**. In press.

[23] Bui, B. H.; Zhu, R. S.; Lin, M. C., *J. Chem. Phys.* **2002**, *117*, 11188.

[24] Bui, B. H.; Schreiner, P. R., *Org. Lett.* **2003**, *5*, 4871.

[25] Schreiner, P. R.; Bui, B. H., *Eur. J. Org. Chem.* **2006**, 1162.

[26] Myers, A. G.; Kuo, E. Y.; Finney, N. S., *J. Am. Chem. Soc.* **1989**, *111*, 8057.

[27] Saito, I.; Nagata, R.; Yamanaka, H.; Okazaki, E., *Tetrahedron Lett.* **1989**, *30(37)*, 4995.

[28] Schmittel, M.; Strittmatter, M.; Kiau, S., *Tetrahedron Lett.* **1995**, *36*, 4975.

[29] Schmittel, M.; Kiau, S.; Siebert, T.; Strittmatter, M., *Tetrahedron Lett.* **1996**, *37*, 7691.

[30] Nakatani, K.; Isoe, S.; Maekawa, S.; Saito, I., *Tetrahedron Lett.* **1994**, *35*, 605.

[31] Sullivan, R. W.; Coghlan, V. M.; Munk, S. A.; Moore, H. W.; Reed, M. W., *J. Org. Chem.* **1994**, *59*, 2276.

CHAPTER 2

BEYOND SCHMITTEL AND MYERS-SAITO CYCLIZATIONS: REARRANGEMENTS OF 4-HETEROATOM-1,2-HEXA-DIENE-5-YNES [1]

[1]Binh H. Bui and Peter R. Schreiner, Copyright (2003) American Chemical Society. The following article appeared in *Org. Lett.*, ***5***, 4871 (2003). The American Chemical Society extends blanket permission to students to include in their theses and dissertations their own articles, or portions thereof, that have been published in ACS journals.

2.1 ABSTRACT

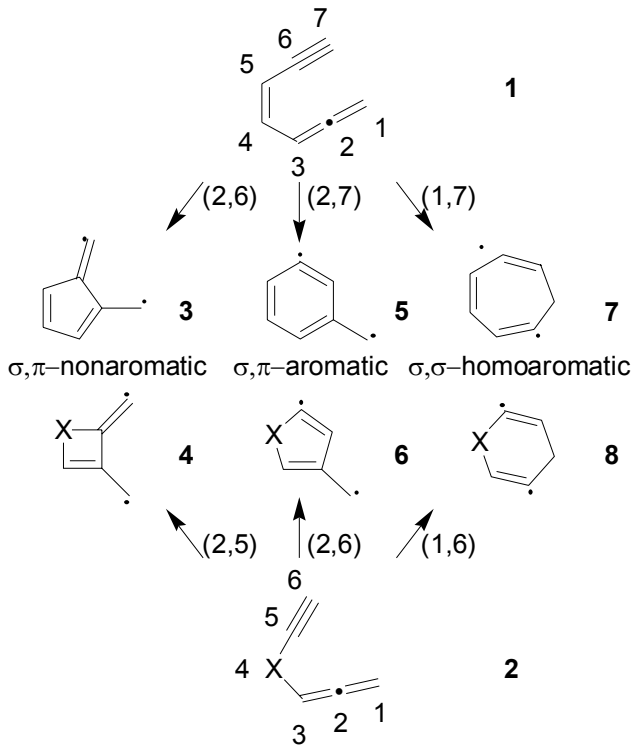
The thermal rearrangements of 4-heteroatom-1,2-hexadiene-5-ynes (**2**) were studied at the BLYP/6-311+G*//BLYP/6-31G* level of theory. Cyclization of **2** to heteroatom-containing cyclopentadienyl structures (**6**) competes with the Claisen-type rearrangement to acyclic, allenic structures. Cyclizations to cyclobutene (**4**)- and cyclohexadiene (**8**)-derived heterocycles are not feasible as a result of high reaction barriers and lower-lying alternative pathways.

2.2 INTRODUCTION

The cyclization reactions of enyne-allenes (parent **1**, Scheme 2.1) lead to biradicals (Myers-Saito C^2–C^7 cyclization,[1, 2] and Schmittel C^2–C^6 cyclization[3, 4, 5, 6, 7]) that display antitumor activity (DNA cleavage)[3, 4, 5, 6, 7, 8] but also provide access to novel polycyclic materials.[9] The 1,7-cyclization has not yet been observed but seems also viable based on previous computational studies.[10] It is surprising, however, that enyne-allenes with heteroatoms in place of the central olefinic bond (such as **2**) have not been examined. As the driving force in some of the more facile reactions of **1** (such as the formation of **5**) is the aromatic product stabilization, the cyclizations of **2** should be energetically viable if **X** provides a lone pair of electrons. We could recently show that this is true for the related Bergman-like cyclization of **9** for **X** = OH^+ (Scheme 2.2) and others.[11, 12]

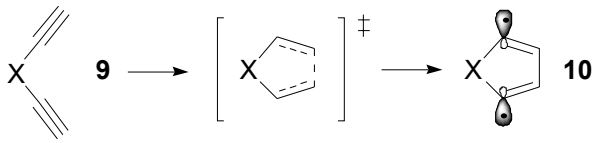
The present Letter aims at examining the biradical cyclization reactions of **2** in a systematic fashion leading to the formally aromatic hetero-cyclopentadien-di-yl **6**, the homoaromatic cyclohexadiene-di-yl **8**, and the nonaromatic cyclobutene derivative **4** (Scheme

2.1). Our expectation is that σ-electron-withdrawing, π-electron-donating **X** groups (for our selection see Figure 2.1) will facilitate the cyclization of **2** to the electron-rich systems **4**, **6**, and **8**. This analysis is based on the study of the endothermic retro Bergman cyclization of 1,3,4,6-tetrafluorohex-3-ene-1,5-diyne where the forward reaction even becomes exothermic when the enediyne substrate is substituted with fluorine in all positions;[13] electron-withdrawing substitutions generally promote the Bergman cyclization.[14, 15]



Scheme 2.1

For three cyclization pathways of **2** (Scheme 2.1), relative activation and reaction energies as functions of **X** are presented in Figures 2.2 and 2.3, respectively. Table 2.1 includes the relative energies as well as the NICS[16] values for the TS's and products. Additional materials can be found in the Supplemental Material.



Scheme 2.2

2.3 METHODS

All computations were performed with the Gaussian 98 software package.[17] Optimizations of all ground-state geometries utilized Becke's pure gradient-corrected ex-change functional[18] (BLYP) and the Lee-Yang-Parr non-local correlation functional[19] (BLYP) with a 6-31G* basis set.[20] A restricted approach was used in the computational analysis for the closed-shell reactants, whereas an unrestricted broken-spin approach (BS-UBLYP) for the open-shell singlet state transition structures (TSs) and products. Analytical vibrational frequencies were calculated for every species to identify the minima, the TSs, and to obtain the zero-point vibrational energies (ZPVE) as well as thermal corrections. Additional single-point energies were evaluated using the same level of theory but with a larger basis set (6-311+G*) for all species. As several studies have shown, for qualitative purposes this level of theory is well-suited to evaluate the experimental feasibility of the title reactions.[21, 22, 23, 24, 25, 26, 27]

2.4 RESULTS AND DISCUSSION

The experimental values for the activation barrier and the reaction enthalpy of the Myers-Saito reaction are 23 and −13 ± 4 kcal mol^{-1}, respectively.[22, 28] Our calculated Gibbs activation barriers for the analogous 2,6-cyclization of **2** (**TS_{26}** of **2**) are in the range of 22–37 kcal mol^{-1}.

The low activation barriers of 23.3 and 21.8 kcal mol^{-1} for $\mathbf{TS_{26}}$ when **X** = NH and NH_2^+, respectively, seem therefore experimentally accessible.

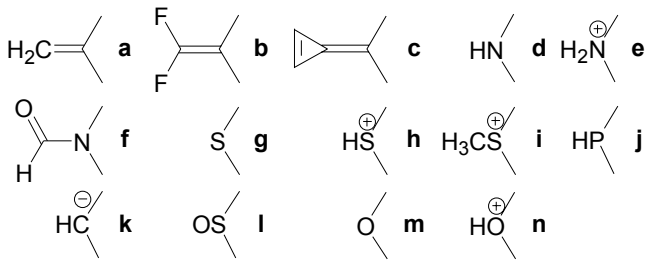
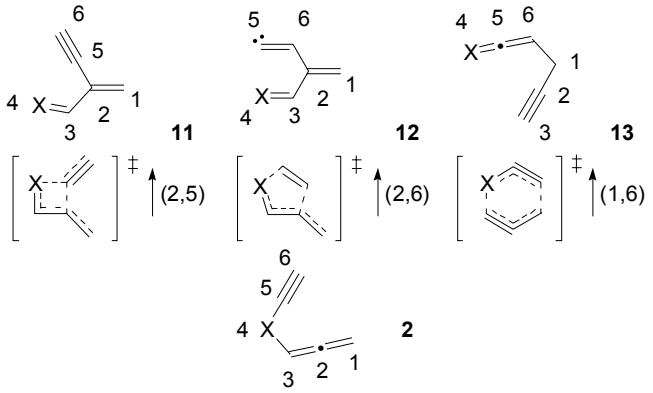


Figure 2.1. Selection of **X** groups for cyclization reactions of **2**.

Surprisingly, the supposedly homoaromatic 1,6-reaction of **2** competes with the 2,6-cyclization. As indicated in Figure 2.2 for **X** = **e**, **g**, **h**, **i**, **j**, **l**, and **m**, the $\mathbf{TS_{16}}$ barriers (*vide infra*) are lower than those of $\mathbf{TS_{26}}$; the 1,6-reaction also is exergonic (Figure 2.3). However, this reaction does not result in the expected 1,6-product **8** but instead gives an acyclic product formally resulting from a Claisen-type rearrangement to form the more stable product **13** (Scheme 2.3).[29, 30, 31, 32] The rearrangement is characterized by highly aromatic TSs as indicated by the negative NICS values at UBLYP/6-311+G* (Table 2.1).



Scheme 2.3

In analogy to the Schmittel reaction[3, 4, 5, 6, 7] of **1** to **3**, there is the 2,5-cyclization of **2** to the nonaromatic cyclobutadiene derivatives **4** (Scheme 2.1). The rather high barriers ($\Delta G^{\ddagger}$ (**TS_{25}**) = 27–48 kcal mol^{-1}) and endergonicities (ΔG(**4**) = 20–63 kcal mol^{-1}) relative to those of the Schmittel cyclization (35 and 10 kcal mol^{-1}, respectively)[22] and the availability of alternative pathways render this reaction highly unlikely. As found for the 1,6-reaction of **2**, several four-membered rings do not even form (**4h**, **i**, **l**, **m**, and **n**) because of the facile C^5-X bond cleavage to the more stable dien-ynes (**11h**, **i, l**, **m**, and **n**, Scheme 2.3).

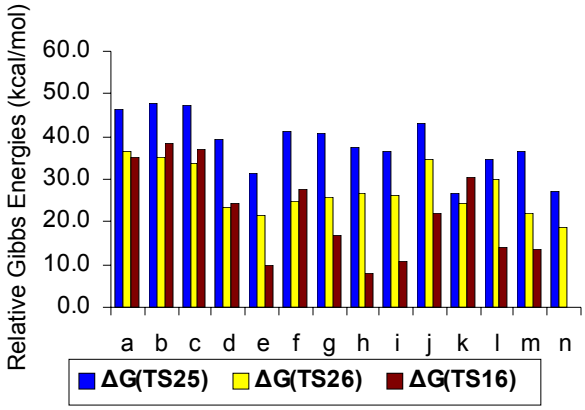


Figure 2.2. Relative Gibbs activation energies (kcal mol^{-1}, at UBLYP/6-31G*) for the thermal cyclization of **2** as a function of **X** to form products **4**, **6**, and **8**.

The frontier molecular orbital (FMO) analysis of the **TS_{26}** family (Scheme 2.4, **X** = NH) describes the transformation of the in-plane π-orbitals into the σ-orbitals (HOMO–1); the rotation of the methylene group in the TS accompanies the cyclization. Therefore, the transition structure's active MOs comprise of π- (HOMO and HOMO–2) and σ-contributors (HOMO–1). As a consequence, choice of **X**-substituents with σ-accepting ability is crucial for reducing the cyclization barriers. Electronegative substituents lower the barriers by withdrawing in-plane

electron density and thus reducing the antibonding character of the σ-π-mixing MO (HOMO−1);[10] this is evident from the formation of **6d**, **6e**, and **6f** (Figure 2.2). As found previously, the amplified electron-accepting ability of the nitrogen due to protonation gives the lowest barrier for the protonated amino function **6e**;[11] this also applies to the lowering of the thiophene reaction barrier (**6h**).

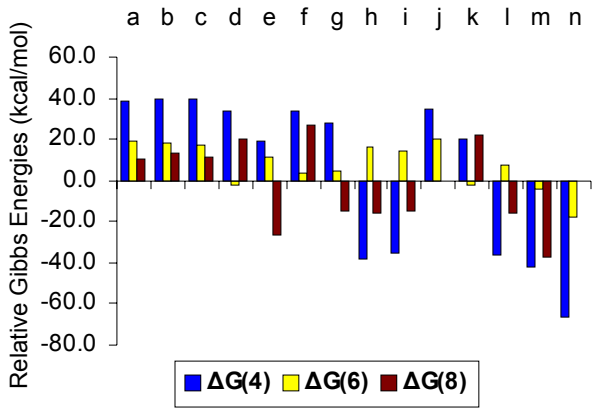


Figure 2.3. Relative Gibbs reaction energies (kcal mol^{-1}, at UBLYP/6-31G*), for the thermal cyclization of **2** as functions of **X** to form products **4**, **6**, and **8**.

However, unlike the exergonicity observed for the Myers-Saito cyclization, the opposite is found for the 2,6-cyclization of **2** (Figure 2.3, ΔG(**6**)) with the exception of **X** = NH, where ΔG(**6**) = −1.8 kcal mol^{-1}. Our expectation that the formation of an aromatic sextet would stabilize the product is apparently not met, despite the fact that the computed NICS values indicate appreciable aromaticity in most products **6** (Table 2.1). For **X** = O, and OH^+, ΔG(**6**) = −3.9 and −17.6 kcal mol^{-1}, respectively, these exergonicities are due to the C^5-X bond cleavage to form the more stable products **12** instead of **6** (Scheme 2.3).

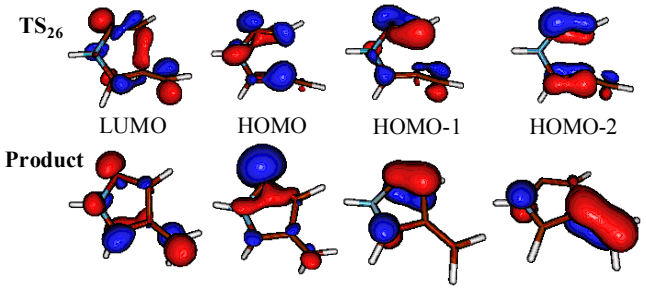
Table 2.1. Relative single point energies (kcal mol^{-1}), and NICS values (in the 4-, 5-, and 6-membered ring centers) at BLYP/6-311+G*//BLYP/6-31G* for the transition structures and products of the thermal cyclization of 4-heteroatom-1,2-diene-5-ynes (**2**).

	BLYP/ 6-311+G*//BLYP/6-31G*					
X	ΔE			NICS		
	TS_{25}	**TS_{26}**	**TS_{16}**	**TS_{25}**	**TS_{26}**	**TS_{16}**
a	50.8	38.3	35.4	–0.8	–5.5	–19.0
b	51.5	36.8	38.0	–2.6	–7.8	–20.4
c	50.6	34.9	37.5	–0.9	–7.9	–19.3
d	41.7	23.6	24.0	–2.1	–12.7	–20.3
e	35.4	23.4	10.6	–5.4	–9.8	–18.3
f	44.2	26.0	28.7	–3.2	–10.8	–18.9
g	42.2	26.1	16.5	–3.2	–13.3	–25.0
h	40.3	27.3	8.1	–3.5	–11.6	–18.9
i	38.9	26.9	10.5	–3.7	–11.2	–22.1
j	45.6	35.3	21.4	–4.2	–9.4	–22.3
k	26.8	22.3	27.3	1.8	–11.0	–15.5
l	36.0	30.6	12.4	–0.9	–11.6	–19.6
m	39.5	24.5	13.9	–1.2	–12.1	–21.8
n	29.5	19.2	n/a	–8.1	–13.2	n/a[a]
			Products:			
	4	**6**	**8**	**4**	**6**	**8**
a	42.6	21.4	9.6	2.7	–3.9	n/a[a]
b	43.1	20.3	11.5	0.6	–6.6	n/a[a]
c	44.0	18.9	10.2	1.5	–5.0	n/a[a]
d	34.8	–3.0	19.9	8.1	–2.0	–17.6
e	24.1	13.2	–26.9	–2.3	–8.7	n/a[a]
f	38.4	4.3	27.5	–0.2	–4.7	–17.3
g	30.9	4.1	–16.0	12.4	–6.1	n/a[a]
h	–39.6	17.7	–16.9	n/a[a]	–9.6	n/a[a]
i	–36.1	15.1	–16.5	n/a[a]	–8.6	n/a[a]
j	37.8	21.7	–0.7	1.5	–6.8	n/a[a]
k	17.9	–6.9	17.9	9.0	5.8	–10.1
l	–39.1	7.2	–19.1	n/a[a]	–8.4	n/a[a]
m	–43.3	–3.3	–40.0	n/a[a]	n/a[a]	n/a[a]
n	–69.1	–18.4	n/a	n/a[a]	n/a[a]	n/a[a]

[a]Unaccounted NICS values for products without ring formation due to either the C^3–X or C^5–X cleavages.

Hence, the substituent's π-donating ability is insufficient to stabilize the cyclic products **6**. Note that most of the **TS_{26}** NICS values are even larger than that of benzene (–7.6) calculated

at the same level of theory. The active MO analysis (Scheme 2.4) supports an early π-delocalized transition structure. Stahl et al.[27] in their study on the aromaticity of the Myers-Saito cyclization reported similar cyclic electron delocalization predominately present in the transition structure π-system that is perpendicular to the molecular plane.



Scheme 2.4. Frontier molecular orbital analysis of the transition structure and product of the 2,6-cyclization of **2** with **X =** NH.

2.5 CONCLUSIONS

We have examined different reaction pathways of 4-heteroatom-1,2-hexadiene-5-ynes (**2**) depending on **X** functional groups. For **X** = **b**, **c**, **d**, **f**, and **k**, of which **k** seems the most appealing the experimental choice, the 2,6-cyclizations of **2** to allylic products **6** should be experimentally accessible as the barriers compare favorably to Myers-Saito reaction of parent **1**. For other functional groups **X** (**a**, **e**, **g**, **h**, **i**, **j**, and **m**) the 1,6-rearrangement of **2** to **13** is energetically preferred. The 2,5-rearrangements have rather high barriers rendering the formations of **4** and **11** unlikely.

2.6 ACKNOWLEDGMENTS

We thank S. Kawatkar for fruitful discussions. This work was supported by National Science Foundation (CHE-0209857). Acknowledgment is also made to the Cherry L. Emerson Center of Emory University for the partial use of its resources, which are supported to B.H.B. by the Department of Energy (DE-FG05-91-ER14192).

2.7 REFERENCES

[1] Saito, I.; Nagata, R.; Yamanaka, H.; Okazaki, E., *Tetrahedron Lett.* **1989**, *30*, 4995.

[2] Myers, A. G.; Kuo, E. Y.; Finney, N. S., *J. Am. Chem. Soc* **1989**, *111*, 8057.

[3] Schmittel, M.; Strittmatter, M.; Kiau, S., *Angew. Chem.* **1996**, *108(16)*, 1952.

[4] Schmittel, M.; Kiau, S.; Siebert, T.; Strittmatter, M., *Tetrahedron Lett.* **1996**, *37(43)*, 7691.

[5] Schmittel, M.; Steffen, J.-P.; Auer, D.; Maywald, M., *Tetrahedron Lett.* **1997**, *38(35)*, 6177.

[6] Schmittel, M.; Keller, M.; Kiau, S.; Strittmatter, M., *Chem. Eur. J.* **1997**, *3(5)*, 807.

[7] Schmittel, M.; Strittmatter, M.; Kiau, S., *Tetrahedron Lett.* **1995**, *36(28)*, 4975.

[8] Chen, P., *Angew. Chem.* **1996**, *108*, 1584.

[9] Schmittel, M.; Strittmatter, M.; Vollmann, K.; Kiau, S., *Tetrahedron Lett.* **1996**, *37(7)*, 999.

[10] Prall, M.; Wittkopp, A.; Schreiner, P. R., *J. Phys. Chem.* **2001**, *105*, 9265.

[11] Kawatkar, S. P.; Schreiner, P. R., *Org. Lett.* **2002**, *4*, 3643.

[12] Lewis, K. D.; Wenzler, D. L.; Matzger, A. J., *Org. Lett.* **2003**, *5*, 2195.

[13] Wenk, H. H.; Balster, A.; Sander, W.; Hrovat, D. A.; Borden, W. T., *Angew. Chem., Int. Ed.* **2001**, *40*, 2295.

[14] Prall, M.; Wittkopp, A.; Fokin, A. A.; Schreiner, P. R., *J. Comput. Chem.* **2001**, *22*, 1605.

[15] Alabugin, I. V.; Manoharan, M., *J. Phys. Chem. A* **2003**, *107*, 3363.

[16] Schleyer, P. v. R.; Maerker, C.; Dransfeld, A.; Jiao, H. J.; Hommes, N., *J. Am. Chem. Soc.* **1996**, *118*, 6317.

[17] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J., J. A. ; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *GAUSSIAN 98, REVISION A. 7*, Gaussian, Inc.: Pittsburgh PA, 1998.

[18] Becke, A. D., *Phys. Rev. A* **1988**, *38*, 3098.

[19] Lee, C. T.; Yang, W. T.; Parr, R. G., *Phys. Rev. B* **1988**, *37*, 785.

[20] Hariharan P. C.; Pople, J. A., *Theor. Chim. Acta* **1973**, *28*, 213.

[21] Engels, B.; Hanrath, M., *J. Am. Chem. Soc.* **1998**, *120*, 6356.

[22] Schreiner, P. R.; Prall, M., *J. Am. Chem. Soc.* **1999**, *121*, 8615.

[23] Cramer, C. J., *J. Am. Chem. Soc.* **1998**, *120*, 6261.

[24] Wenthold, P. G.; Lipton, M. A., *J. Am. Chem. Soc.* **2000**, *122*, 9265.

[25] Graefenstein, J.; Kraka, E.; Filatov, M.; Cremer, D., *Int. J. Mol. Sci.* **2002**, *3*, 360.

[26] Gräfenstein, J.; Hjerpe, A. M.; Kraka, E.; Cremer, D., *J. Phys. Chem. A* **2000**, *104*, 1748.

[27] Stahl, F.; Moran, D.; Schleyer, P. v. R.; Prall, M.; Schreiner, P. R., *J. Org. Chem.* **2002**, *67*, 1453.

[28] Myers, A. G.; Dragovich, P. S.; Kuo, E. Y., *J. Am. Chem. Soc.* **1992**, *114*, 9369.

[29] Hopf, H., *Chem. Ber.* **1971**, *104*, 1499.

[30] Hopf, H., *Tetrahedron Lett.* **1972**, *34*, 3571.

[31] Black, K. A.; Wilsey, S.; Houk, K. N., *J. Am. Chem. Soc.* **1998**, *120*, 5622.

[32] Meijer, J.; Brandsma, L., *Recl. Trav. Chim.* **1972**, *91*, 578.

2.8 SUPPLEMENTAL MATERIAL

for

BEYOND SCHMITTEL AND MYERS-SAITO CYCLIZATIONS: REARRANGEMENTS OF 4-HETEROATOM-1,2-HEXA-DIENE-5-YNES

Binh H. Bui and Peter R. Schreiner[1]

Department of Chemistry University of Georgia, Athens, Georgia 30602-2525

[1] E-mail: prs@chem.uga.edu; prs@org.chemie.uni-giessen.de

Table 2.2. Slater determinant expectation values of (<S2>), enthalpies, Gibbs energies (kcal mol^{-1}) at BLYP/6-31G*, relative single point energies (kcal mol^{-1}), and NICS values (in the 4-, 5-, and 6-membered ring centers) at BLYP/6-311+G* for the transition structures and products of the thermal cyclization of 4-heteroatom-1,2-diene-5-ynes (**2**).

				BLYP/6-31G*									BLYP/ 6-311+G*					
X	$<S^2>$			ΔE			ΔH^0 (298K)			ΔG (298K)			ΔE			NICS		
	TS_{25}	**TS_{26}**	**TS_{16}**	**TS_{25}**	**TS_{26}**	**TS_{16}**	**TS_{25}**	**TS_{26}**	**TS_{16}**	**TS_{25}**	**TS_{26}**	**TS_{16}**	**TS_{25}**	**TS_{26}**	**TS_{16}**	**TS_{25}**	**TS_{26}**	**TS_{16}**
a	0.46	0.00	0.00	47.6	35.8	34.2	45.3	34.8	33.3	46.5	36.7	35.2	50.8	38.3	35.4	–0.8	–5.5	–19.0
b	0.44	0.00	0.00	48.9	34.3	37.2	46.8	33.3	36.4	48.0	35.3	38.2	51.5	36.8	38.0	–2.6	–7.8	–20.4
c	0.36	0.00	0.00	47.9	32.8	36.3	45.9	31.9	35.3	47.2	33.9	37.1	50.6	34.9	37.5	–0.9	–7.9	–19.3
d	0.00	0.00	0.00	38.8	21.5	22.3	37.2	20.8	21.4	39.3	23.3	24.3	41.7	23.6	24.0	–2.1	–12.7	–20.3
e	0.34	0.00	0.00	31.9	20.6	10.6	29.7	19.5	8.7	31.4	21.8	9.7	35.4	23.4	10.6	–5.4	–9.8	–18.3
f	0.15	0.00	0.00	41.6	23.8	26.7	39.8	22.9	25.7	41.1	24.9	27.8	44.2	26.0	28.7	–3.2	–10.8	–18.9
g	0.16	0.00	0.00	40.3	24.0	15.7	38.7	23.2	14.8	40.6	25.7	16.7	42.2	26.1	16.5	–3.2	–13.3	–25.0
h	0.35	0.00	0.00	38.1	25.3	8.2	35.6	24.1	6.8	37.4	26.6	7.9	40.3	27.3	8.1	–3.5	–11.6	–18.9
I	0.31	0.00	0.00	36.8	24.7	10.3	34.7	23.8	9.3	36.4	26.4	10.6	38.9	26.9	10.5	–3.7	–11.2	–22.1
j	0.29	0.00	0.00	43.4	32.9	20.3	41.3	32.2	19.6	43.2	34.6	22.1	45.6	35.3	21.4	–4.2	–9.4	–22.3
k	0.00	0.00	0.00	26.6	23.3	28.9	25.5	22.6	28.3	26.8	24.3	30.7	26.8	22.3	27.3	1.8	–11.0	–15.5
l	0.00	0.00	0.00	34.9	28.8	13.1	33.1	27.7	12.1	34.9	30.0	13.9	36.0	30.6	12.4	–0.9	–11.6	–19.6
m	0.00	0.00	0.00	36.7	21.9	14.5	35.1	20.7	13.0	36.7	22.2	13.5	39.5	24.5	13.9	–1.2	–12.1	–21.8
n	0.11	0.00	0.00	26.1	16.3	n/a	24.5	15.6	n/a	27.4	18.9	n/a	29.5	19.2	n/a	–8.1	–13.2	n/a
Product	**4**	**6**	**8**	**4**	**6**	**8**	**4**	**6**	**8**	**4**	**6**	**8**	**4**	**6**	**8**	**4**	**6**	**8**
a	1.04	1.03	0.00	38.1	16.9	10.8	36.9	17.0	11.0	38.3	19.0	10.4	42.6	21.4	9.6	2.7	–3.9	n/a
b	1.04	1.03	0.00	39.3	16.0	14.1	38.4	16.2	14.6	39.6	17.9	13.8	43.1	20.3	11.5	0.6	–6.6	n/a
c	1.03	0.84	0.00	39.6	15.1	11.5	38.5	15.2	11.9	39.9	17.4	11.4	44.0	18.9	10.2	1.5	–5.0	n/a
d	0.18	0.04	0.00	32.4	–5.9	17.2	31.3	–5.0	17.4	33.3	–1.8	20.2	34.8	–3.0	19.9	8.1	–2.0	–17.6
e	1.03	0.83	0.00	19.5	8.5	–26.2	17.9	8.4	–26.4	19.6	11.0	–26.1	24.1	13.2	–26.9	–2.3	–8.7	n/a
f	1.03	0.28	0.00	34.6	1.1	25.0	33.3	1.5	24.9	34.2	4.0	27.0	38.4	4.3	27.5	–0.2	–4.7	–17.3
g	1.03	0.33	0.00	27.4	1.3	–16.3	26.4	1.9	–15.3	28.2	4.9	–14.9	30.9	4.1	–16.0	12.4	–6.1	n/a
h	0.00	0.87	0.00	–40.9	14.0	–16.0	–39.8	13.6	–15.7	–38.4	16.2	–15.4	–39.6	17.7	–16.9	n/a	–9.6	n/a
I	0.00	0.84	0.00	–37.1	11.3	–15.5	–36.0	11.6	–14.9	–35.5	14.5	–15.3	–36.1	15.1	–16.5	n/a	–8.6	n/a
j	1.03	1.02	0.00	34.1	17.5	–1.5	32.9	17.5	–0.8	34.9	19.8	–0.3	37.8	21.7	–0.7	1.5	–6.8	n/a

k	0.00	0.00	0.00	18.9	–6.0	18.9	18.9	–4.9	19.7	20.5	–2.6	22.2	17.9	–6.9	17.9	9.0	5.8	–10.1
l	0.00	0.00	0.00	–38.5	6.1	–17.3	–37.6	6.3	–16.3	–36.4	7.7	–16.2	–39.1	7.2	–19.1	n/a	–8.4	n/a
m	0.00	0.00	0.00	–42.9	–6.0	–38.0	–42.5	–5.6	–37.4	–41.8	–3.9	–37.5	–43.3	–3.3	–40.0	n/a	n/a	n/a
n	0.00	0.00	0.00	–70.8	–21.2	–36.7	–68.7	–20.2	–35.9	–66.2	–17.6	–34.7	–69.1	–18.4	–37.0	n/a	n/a	n/a

CHAPTER 3

MOORE CYCLIZATIONS: REARRANGEMENTS OF 3-HETEROATOM-PENT-1-EN-4-YN-1-ONES - A COMPUTATIONAL SEARCH FOR NEW REACTIONS [2]

[2]Binh H. Bui and Peter R. Schreiner, Copyright (2006) Wiley-VCH Verlag GmbH & Co. The following article appeared in *Eur. J. Org. Chem.*, ***5***, 1162 (2006). The VCH-RIGHTS-and-LICENCES grants permission to students to include in their theses and dissertations their own articles, or portions thereof, with expectation of due credit given to the original source.

3.1 ABSTRACT

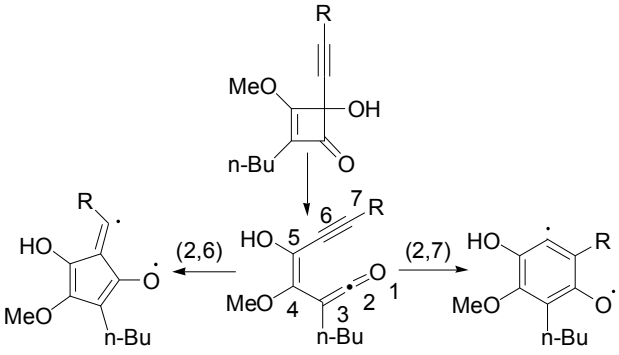
The thermal rearrangements of 3-heteroatom-pent-1-en-4-yn-1-ones (**2**) were studied at the BLYP/6-311+G*//BLYP/6-31G* level of theory. While cyclizations of (**2**) to oxo-hetero-cyclopentadien-di-yl (**6**) are most favorable and predicted to be experimentally feasible for X = CH^-, NH, O, and S, protonation of these substituents raises the corresponding 2,6-cyclization barriers. Cyclizations to oxacyclohexadiendiyl (**8**) are highly improbable due to competition with other low-lying alternative pathways.

3.2 INTRODUCTION

New chemical reactions are by and large discovered through serendipity and not–although some of us may naturally disagree–through systematic strategies. Computational methods can in principle be used to truly predict new reactions but this is rarely done in practice because it is dangerous to make bold predictions that can readily be tested. As we have demonstrated recently that one can indeed computationally predict new reactions *if* they come out of a *reaction family* [1, 2] (i.e. they are very closely related) we apply this heuristic approach also to the cyclizations of enyne-ketenes in the present study.

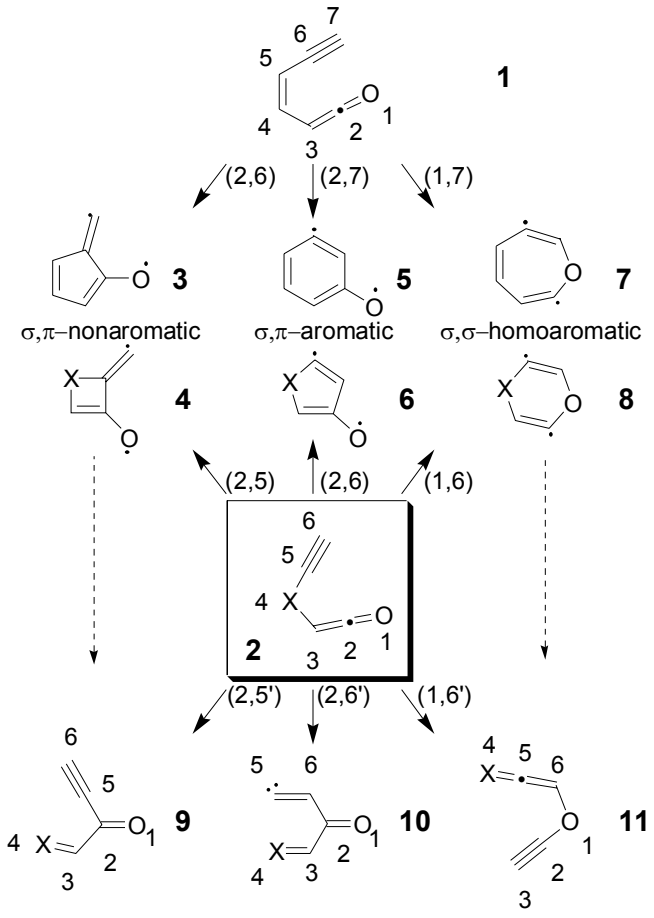
(2-Alkynyl ethynyl) ketene (Scheme 3.1) generated *in-situ* from the selective ring opening of 4-alkynylcyclobutenone[1, 2, 3] undergoes C^2–C^6 or C^2–C^7 cyclization to form five- and six-membered cyclic products, respectively.[4] Various substituents **R** have been probed experimentally to control the direction of the cyclizations; radical-stabilizing substituents **R**, such as alkoxy, phenyl, and trimethylsilyl, favor the 2,6-pathway and give five-membered rings.[4]

These reactions are assumed to involve diradical intermediates that are candidates for DNA cleavage.[5, 6] Engels et al. computationally examined the biradical routes of these so-called Moore cyclizations of parent **1** (Scheme 3.2) to cyclic products **3** and **5**.[7] No study has been reported for the 1,7-reaction path (Scheme 3.2) leading to oxacycle **7** (oxepins), which are common in biologically active natural products.[8, 9, 10, 11] Enyne-ketenes that are analogous to **2** with heteroatoms in place of the central olefinic bond have not been examined with respect to their cycloaromatizations akin to **1** (Scheme 3.2). The present work reports a systematic study of **2** as a building block for a new "reaction family"[12, 13, 14, 15, 16] and provides firm predictions regarding the formation of heterocycles through novel hetero-Moore reactions.



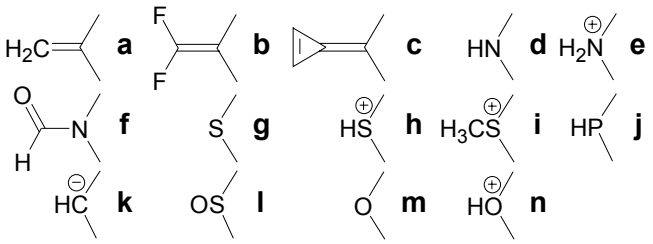
Scheme 3.1

Previous studies on the rearrangements of heteroatom-substituted enyne-allenes[15] revealed the importance of **X** in donating its electron lone pair into the terminal methylene group; this effect overrides aromatic stabilization in the five-membered ring products. The σ-electron-withdrawing ability of **X** promotes the cyclizations by reducing the electron density from the electron-rich in-plane-π systems.[14, 15] For the current analysis of **2**, the choice of **X** is also crucial because the initially unfavorable 2 + 2 addition of the 2,6-cyclization requires **X** to



Scheme 3.2

be a σ-acceptor;[17, 18] yet, the perpendicular π-system demands **X** to have an electron pair in conjugation with the molecular π-system to provide an aromatic sextet. With respect to **X**'s π-donating and σ-accepting abilities, various **X**s (Scheme 3.3) were considered. We systematically present the cyclizations of **2** to the *nonaromatic* oxo-hetero-cyclobutene derivative **4**, the formally *aromatic* oxo-hetero-cyclopentadiendiyl **6**, and the *homoaromatic* oxa-cyclohexadiendiyl **8** (Scheme 3.2). Competing pathways such as the rearrangement of **2** to acyclic but-yn-ones (**9**) and but-en-ones (**10**), and the formal hetero-Claisen reactions of **2** to en-ethynyloxy products **11** were also examined.[12, 13]



Scheme 3.3. Selection of **X** groups for cyclization reactions of **2**.

3.3 METHODS

Becke's pure gradient-corrected exchange functional[19] in conjunction with the Lee-Yang-Parr non-local correlation functional (BLYP)[20] and the 6-31G* basis set were utilized for all optimizations as implemented in Gaussian03.[21] Open-shell singlet state transition structures (TSs) and products were computed with a broken-spin approach (UBS-BLYP), while all closed-shell species were computed with the restricted method. Thermal corrections and zero-point vibrational energies (ZPVE) were determined by evaluating analytical second derivatives to characterize minima and transition structures. Additional single-point energies with the same functional but with a larger basis set (6-311+G*) were also computed for all species. UBS DFT has been a practical tool to provide good qualitative results for cyclizations of polyunsaturated systems.[12, 13, 14, 15, 22, 23, 24, 25, 26, 27, 28] Elaborate multireference calculations are currently too time-consuming for the large number of structures considered in the present study. Single-point Brueckner Doubles computations (BD(T))[29, 30] with a cc-pVDZ basis set using the DFT geometries were computed for comparison in critical cases.

Table 3.1. Thermal rearrangements of **2** as a function of **X**: dark, medium, and light gray colors coded for the 2,5-, 2,6-, and 1,6-reaction, respectively; relative Gibbs activation ($\Delta G^{\ddagger}$, normal) and reaction free energies (ΔG, *italics*) at UBLYP/6-31G*) shown only for energetically favorable or competitive pathways (in kcal mol^{-1}).

Products / **X**	**4**	**6**	**8**	**9**	**10**	**11**
a	x[a]	34.8 *29.4*	n/a[b]	n/a[b]	n/a[b]	x[a]
b	x[a]	34.6 *26.9*	n/a[b]	n/a[b]	n/a[b]	x[a]
c	x[a]	31.9 *22.7*	n/a[b]	n/a[b]	n/a[b]	x[a]
d	x[a]	23.4 *6.9*	x[a]	n/a[b]	n/a[b]	n/a[b]
e	x[a]	30.4 *22.4*	n/a[b]	n/a[b]	n/a[b]	x[a]
f	x[a]	26.6 *12.3*	x[a]	n/a[b]	n/a[b]	n/a[b]
g	x[a]	32.2 *17.8*	n/a[b]	n/a[b]	n/a[b]	x[a]
h	n/a[b]	39.1 *33.4*	n/a[b]	38.1 *–12.5*	n/a[b]	36.3 *26.3*
i	n/a[b]	37.4 *32.1*	n/a[b]	36.2 *–10.7*	n/a[b]	36.6 *25.8*
j	n/a[b]	38.3 *33.6*	n/a[b]	x[a]	n/a[b]	x[a]
k	19.9 *14.1*	19.2 *–5.5*	x[a]	n/a[b]	n/a[b]	n/a[b]
l	n/a[b]	n/a[b]	n/a[b]	16.7 *–21.1*	x[a]	x[a]
m	x[a]	19.6 *2.6*	x[a]	n/a[b]	n/a[b]	n/a[b]
n	n/a[b]	x[a]	n/a[b]	23.4 *–54.1*	n/a[b]	10.5 *–3.4*

[a] Unlisted energetics for kinetically (barriers > 40 kcal mol^{-1}) or thermodynamically (endergonicities > 40 kcal mol^{-1}) highly unfavorable products. [b] Not accessible from the direct thermal rearrangements of **2**.

3.4 RESULTS AND DISCUSSION

In the reactions (TS_{xy}) of **2** as a function of **X**, products **4**, **6**, and **8** are accompanied by competing rearrangements (TS_{xy}') giving rise to acyclic products **9**, **10**, and **11** (Scheme 3.2); the prime indicates reaction paths leading to acyclic products. Existing reaction paths are coded by colors, i. e., dark, medium, and light gray colors, assigned to 2,5- (or 2,5'), 2,6- (or 2,6'-), and 1,6- (or 1,6'-) reactions, respectively (Table 3.1). Energetics are only shown for the most favorable or competitive reactions. Table 3.2 provides relative energies at BLYP/6-311+G**//BLYP/6-31G* + ZPVE/6-31G* as well as the NICS[31] values for all cyclic species.

Although the experimental thermodynamics of the Moore cyclizations of parent **1** have not been determined,[5] Engels et al. reported computed Gibbs activation barriers for the C^2–C^6 and C^2–C^7 cyclizations of 41.4 and 13.6 kcal mol^{-1}, respectively, using the B3LYP/6-31G(d) level of theory. The corresponding reaction energies are 24.8 and 4.8 kcal mol^{-1}; clearly, the C^2–C^7 ring closure is kinetically and thermodynamically favored. For the analogous 2,6-cyclizations of **2** (Scheme 3.2) our computed Gibbs activation barriers (BLYP/6-31G(d)) have a range of 19–39 kcal mol^{-1}, indicating the experimental feasibility (some at high temperatures only) of these heteroatom-substituted reactions (**X** = **k**, **m**, and **d**). Although the lowest barrier (**TS_{26}**) of 19.2 for **X** = **k** is 5.6 kcal mol^{-1} higher than that of **TS_{27}** of parent **1**, the 2,6-reaction of **2** is thermodynamically favored as indicated by the computed exergonicity (ΔG (**6**) = –5.5 kcal mol^{-1}). Note that the 2,6- and 2,7-cyclizations of the parent **1** are thermodynamically unfavorable.

Table 3.2. Relative single point energies (kcal mol^{-1}), and NICS values (in the 4-, 5-, and 6-membered ring centers) at BLYP/6-311+G*//BLYP/6-31G* + ZPVE for the TSs and products of the thermal cyclization of 3-heteroatom-pent-1-ene-4-yn-1-ones (**2**).

	BLYP/ 6-311+G*//BLYP/6-31G* + ZPVE					
X	ΔE			NICS		
	TS_{25}	**TS_{26}**	**TS_{16}**	**TS_{25}**	**TS_{26}**	**TS_{16}**
a	53.5	37.8	63.3	74.3	–5.6	–20.8
b	51.6	37.4	67.3	17.0	–6.4	–21.9
c	44.9	33.9	61.0	30.5	–6.3	–20.4
d	38.1	25.2	36.6	6.2	–9.8	–17.6
e	53.9	32.5	30.9	–3.6	–5.5	–21.4
f	39.4	28.6	43.2	13.9	–8.3	–16.0
g	40.1	33.3	41.0	10.5	–9.9	–22.1
h	41.2	40.8	37.4	3.9	–6.8	–23.9
i	38.7	39.2	37.8	3.9	–6.7	–23.4
j	44.1	40.0	50.4	1.8	–9.3	–18.8
k	17.3	17.7	26.1	0.3	–9.0	–13.4
l	17.6	36.1	30.0	–8.8	–5.0	–17.9
m	32.1	21.9	37.8	14.4	–8.8	–19.1
n	26.6	29.2	11.9	2.2	–6.3	–14.1
	Products:					
	4	**6**	**8**	**4**	**6**	**8**
a	48.3	32.9	*47.4*	11.3	2.0	n/a[a]
b	47.1	30.9	*52.3*	7.3	0.1	n/a[a]
c	42.6	25.7	*47.0*	30.5	0.1	n/a[a]
d	36.1	10.0	37.5	5.9	4.1	–14.3
e	35.0	26.1	*13.0*	11.2	–3.1	n/a[a]
f	38.7	16.4	44.1	4.1	–3.4	–14.2
g	33.7	22.9	*31.2*	2.8	–5.2	n/a[a]
h	*–11.6*	36.3	*27.7*	n/a[a]	–3.8	n/a[a]
i	*–9.6*	34.9	*27.7*	n/a[a]	–3.7	n/a[a]
j	*6.8*	36.2	*44.1*	n/a[a]	–2.9	n/a[a]
k	12.4	–6.2	24.1	15.0	9.9	–6.6
l	*–21.7*	*20.5*	*22.5*	n/a[a]	n/a[a]	n/a[a]
m	26.0	6.6	39.4	6.2	–5.2	–15.9
n	*–51.9*	14.5	*0.0*	n/a[a]	–6.0	n/a[a]

[a] Unaccounted NICS values for products without ring formation due to either the C^3–X or C^5–X cleavages; this also indicates that their corresponding TSs lead to acyclic products (**9**, **10**, and **11**), whose energies are listed *italically*.

For the reaction leading to cyclic products **4**, **6**, and **8**, the "aromatic" 2,6-reaction of **2** dominates over the nonaromatic 2,5- and homoaromatic 1,6-reactions both kinetically and

thermodynamically; there are only a few exceptions. For **X** = **k**, the 2,5-reaction competes kinetically with the 2,6-reaction. With **X** = **h**, **i**, **l**, and **n**, the $\mathbf{TS_{25}}$**'** barriers are lower than those of the 2,6-cyclizations ($\mathbf{TS_{26}}$); the former reactions are also exergonic because stable acyclic ene-yne ketone products (**9**) result (Table 3.1).

High barriers for **X** = **f**, **m**, **d**, and **k** prevent the 1,6-cyclizations of **2**. Instead, **2** undergoes Claisen-type 1,6'-rearrangement cleaving the $\mathbf{C^3}$**-X** bond to give acyclic **11**. Although for **X** = **e**, **h**, **i**, **l**, and **n** the Claisen-like reaction barriers ($\mathbf{TS_{16}}$**'**) and the reaction energies (ΔG(**11**)) are energetically below those of aromatic 2,6-reactions [ΔG($\mathbf{TS_{26}}$) and the ΔG(**6**)], this 1,6'-pathway competes with the 2,5'-reaction path forming the acyclic product **9** (vide infra). Therefore, except for **X** = **e** the 1,6'-reactions of **2** are highly improbable.

The dominance of the aromatic 2,6-cyclization path can be understood by analyzing its frontier molecular orbitals (FMOs). Figure 3.1 presents the FMOs study of $\mathbf{TS_{26}}$ with **X** = $\mathbf{CH^-}$ (= **k**) describing the transformation of the in-plane π-orbitals into the σ-orbitals (HOMO-2). Unlike the Myers-Saito reaction in which the methylene group rotates during the cyclization, the electronegative oxygen atom strongly polarizes the TS. The oxygen atom not only dispels the antibonding character of the σ-π-mixing MO across the C–C bond formation (HOMO-2) of the transition structure, but also withdraws the electron density across the π-MO perpendicular to the molecular plane (HOMO-1). While the former effect results in a significant reduction of the C^2–C^6 activation barrier of **2** (vide infra), the latter diminishes the aromatic-sextet stabilization expected in product **6**.

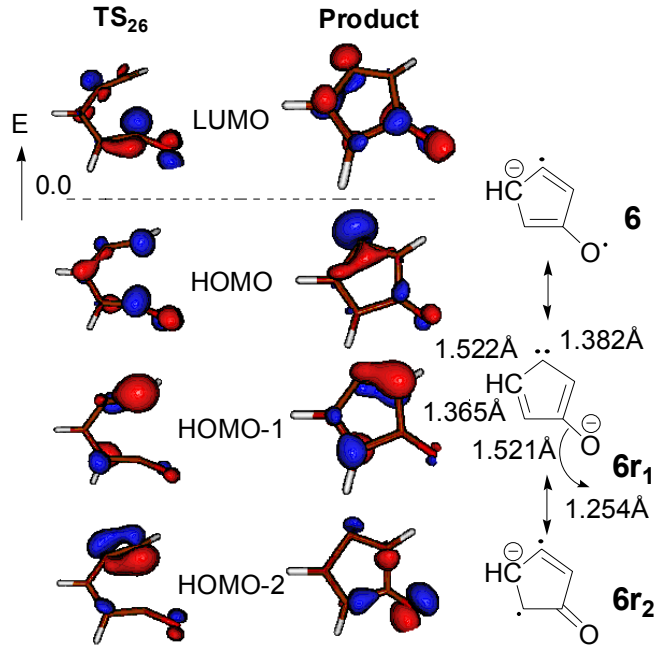


Figure 3.1. Frontier molecular orbital analysis of the transition structure and product of the 2,6-cyclization of **2** with **X** = CH^-.

Additionally, the bond lengths of C=O (1.254 Å) and C=X (1.365 Å, Figure 3.1) support the resonance forms of **6** (**6**↔**6r**$_1$↔**6r**$_2$, Figure 3.1). This can be seen in HOMO and HOMO-1 where the mixing is visible between the σ- and π-MOs. However, the notion of an aromatic sextet stabilizing the product, i. e., **X** providing a lone pair of electrons during the C^2–C^6 cyclization, is not corroborated by the computed thermodynamic stabilization. The contribution of the **X** lone pair can be turned off by protonation, i. e., **X** = **d**, **g**, and **m** versus **e**, **h**, and **n**. As a consequence, the Gibbs activation barriers of the protonated forms (ΔG(**TS**$_{26}$)) are uniformly higher by about 7.0 kcal mol^{-1} (Table 3.1), resulting from the inability to form an aromatic electron sextet or stable resonance forms.

3.5 CONCLUSIONS

We conclude that out of the very many reactions possible for the cyclizations or rearrangements of starting heteroatom ketene-alkyne **2**, only very few are chemically relevant: with some rare exceptions, *aromatization* reactions to hetero-substituted furans **6** are preferred, irrespective of the heteroatom and the charge state. Hence, this "heuristic" approach to identifying new chemical reactions by means systematic computational comparisons of available reactions pathways helps to predict novel transformations that now await experimental verification. As many of the starting materials of **2** can be readily prepared (e.g., X = **k** or **m**), this is a realistic goal.

3.6 ACKNOWLEDGMENTS

We thank Dr. A. Navarro-Váquez and Dr. A. A. Fokin for valuable discussions. This work was supported by National Science Foundation (CHE-0209857) and the Department of Energy (DE-FG05-91-ER14192).

3.7 REFERENCES

[1] Perri, S. T.; Dyke, H. J.; Moore, H. W., *J. Org. Chem.* **1989**, *54*, 2032.

[2] Perri, S. T.; Foland, L. D.; Moore, H. W., *Tetrahedron Lett.* **1988**, *29*, 3529.

[3] Karlsson, J. O.; Nguyen, N. V.; Foland, L. D.; Moore, H. W., *J. Am. Chem. Soc* **1985**, *107*, 3392.

[4] Foland, L. D.; Karlsson, J. O.; Perri, S. T.; Schwabe, R.; Xu, S. L.; Patil, S.; Moore, H. W., *J. Am. Chem. Soc* **1989**, *111*, 975.

[5] Sullivan, R. W.; Coghlan, V. M.; Munk, S. A.; Moore, H. W.; Reed, M. W., *J. Org. Chem.* **1994**, *59*, 2276.

[6] Nakatani, K.; Isoe, S.; Maekawa, S.; Saito, I., *Tetrahedron Lett.* **1994**, *35*, 605.

[7] Musch, P. W.; Remenyi, C.; Helten, H.; Engels, B., *J. Am. Chem. Soc.* **2002**, *124*, 1823.

[8] Shimizu, M., Fujimoto, T. , Liu, X., Hiyama, T., *Chem. Lett.* **2004**, *33*, 438.

[9] Hoberg, J. O., *Tetrahedron* **1998**, *54*, 12631.

[10] Boyd, D. R., (1984) *in "Comprehensive Heterocyclic Chemistry"*. Oxford: Pergamon Press.

[11] Belen'kii, L. I., (1996) *in "Comprehensive Heterocyclic Chemistry"*. Oxford: Pergamon Press.

[12] Schreiner, P. R.; Navarro-Vázquez, A.; Prall, M., *Acc. Chem. Res.* **2005**, *38*, 29.

[13] Navarro-Vazquez, A.; Prall, M.; Schreiner, P. R., *Org. Lett.* **2004**, *6*, 2981.

[14] Kawatkar, S. P.; Schreiner, P. R., *Org. Lett.* **2002**, *4*, 3643.

[15] Bui, B. H.; Schreiner, P. R., *Org. Lett.* **2003**, *5*, 4871.

[16] Hopf, H., (2000) *Classics in Hydrocarbon Chemistry*. Weinheim: Wiley-VCH.

[17] Alabugin, I. V.; Manoharan, M.; Kovalenko, S. V., *Org. Lett.* **2002**, *4*, 1119.

[18] Koga, N.; Morokuma, K., *J. Am. Chem. Soc.* **1991**, *113*, 1907.

[19] Becke, A. D., *Phys. Rev. A* **1988**, *38*, 3098.

[20] Lee, C. T.; Yang, W. T.; Parr, R. G., *Phys. Rev. B* **1988**, *37*, 785.

[21] Frisch, M. J., et al. *GAUSSIAN 03, REVISION B.03*, Gaussian, Inc.: Pittsburgh PA, 2003.

[22] Engels, B.; Hanrath, M., *J. Am. Chem. Soc* **1998**, *120*, 6356.

[23] Stahl, F.; Moran, D.; Schleyer, P. V.; Prall, M.; Schreiner, P. R., *J. Org. Chem.* **2002**, *67*, 1453.

[24] Gräfenstein, J.; Hjerpe, A. M.; Kraka, E.; Cremer, D., *J. Phys. Chem. A* **2000**, *104*, 1748.

[25] Gräfenstein, J.; Kraka, E.; Filatov, M.; Cremer, D., *Int. J. Mol. Sci.* **2002**, *3*, 360.

[26] Wenthold, P. G.; Lipton, M. A., *J. Am. Chem. Soc* **2000**, *122*, 9265.

[27] Cramer, C. J., *J. Am. Chem. Soc* **1998**, *120*, 6261.

[28] Schreiner, P. R.; Prall, M., *J. Am. Chem. Soc* **1999**, *121*, 8615.

[29] Handy, N. C.; Pople, J. A.; Head-Gordon, M.; Raghavachari, K., *Chem. Phys. Lett.* **1989**, *164*, 185.

[30] Crawford, T. D.; Kraka, E.; Stanton, J. F.; Cremer, D., *J. Chem. Phys.* **2001**, *114*, 10638.

[31] Schleyer, P. v. R.; Maerker, C.; Dransfeld, A.; Jiao, H. J.; Hommes, N., *J. Am. Chem. Soc.* **1996**, *118*, 6317.

3.8 SUPPLEMENTAL MATERIAL

for

MOORE CYCLIZATIONS: REARRANGEMENTS OF 3-HETEROATOM-PENT-1-EN-4-YN-1-ONES - A COMPUTATIONAL SEARCH FOR NEW REACTIONS

Binh H. Bui and Peter R. Schreiner[1]

Department of Chemistry University of Georgia, Athens, Georgia 30602-2525

[1] E-mail: prs@chem.uga.edu; prs@org.chemie.uni-giessen.de

Table S1. Slater determinant expectation values of (<S2>), enthalpies, Gibbs energies (kcal mol^{-1}) at BLYP/6-31G*, relative single point energies (kcal mol^{-1}), and NICS values (in the 4-, 5-, and 6-membered ring centers) at BLYP/6-311+G* for the transition structures and products of the thermal cyclization of 3-heteroatom-pent-1-en-4-yn-1-ones (**2**).

							BLYP/6-31G*									**BLYP/ 6-311+G***		
X	<S^2>			ΔE			ΔH^0 (298K)			ΔG (298K)			ΔE			NICS		
	TS_{25}	**TS_{26}**	**TS_{16}**	**TS_{25}**	**TS_{26}**	**TS_{16}**	**TS_{25}**	**TS_{26}**	**TS_{16}**	**TS_{25}**	**TS_{26}**	**TS_{16}**	**TS_{25}**	**TS_{26}**	**TS_{16}**	**TS_{25}**	**TS_{26}**	**TS_{16}**
a	1.03	0.17	0.00	52.0	34.1	62.8	50.0	32.8	60.9	51.2	34.8	61.7	55.0	38.3	65.0	74.3	–5.6	–20.8
b	1.02	0.15	0.00	49.3	33.7	66.8	47.7	32.6	65.1	49.0	34.6	65.9	52.7	37.7	68.7	17.0	–6.4	–21.9
c	1.02	0.00	0.00	44.3	30.5	61.8	42.9	29.6	59.9	44.5	31.9	59.0	45.6	33.9	63.0	30.5	–6.3	–20.4
d	0.67	0.00	0.00	34.8	21.2	29.8	32.9	20.5	29.3	35.1	23.4	33.1	39.2	24.8	35.5	6.2	–9.8	–17.6
e	1.01	0.26	0.00	53.8	29.5	31.9	51.4	27.9	29.2	52.5	30.4	30.2	55.9	33.1	33.4	–3.6	–5.5	–21.4
f	1.01	0.00	0.00	40.1	25.4	37.2	38.6	24.4	36.4	40.3	26.6	39.4	40.2	28.7	42.7	13.9	–8.3	–16.0
g	0.64	0.00	0.00	39.3	30.9	40.4	37.4	29.8	39.1	38.9	32.2	40.2	41.5	33.4	42.0	10.5	–9.9	–22.1
h	0.50	0.12	0.00	39.3	38.2	36.4	36.4	36.5	34.7	38.1	39.1	36.3	43.6	41.6	38.7	3.9	–6.8	–23.9
I	0.47	0.09	0.00	37.4	36.3	36.5	34.9	34.8	35.1	36.2	37.4	36.6	40.8	39.8	38.8	3.9	–6.7	–23.4
j	0.00	0.00	0.00	43.3	36.6	49.2	41.2	35.5	47.7	43.0	38.3	49.4	45.6	40.1	51.4	1.8	–9.3	–18.8
k	0.10	0.00	0.00	21.1	18.4	23.7	19.4	17.6	23.3	19.9	19.2	25.9	18.7	17.9	25.4	0.3	–9.0	–13.4
l	0.00	0.00	0.00	16.4	33.6	30.3	15.3	32.3	29.0	16.7	34.5	30.1	18.2	36.5	30.9	–8.8	–5.0	–17.9
m	0.65	0.00	0.00	29.9	18.2	32.4	27.8	17.1	31.2	29.5	19.6	34.2	33.5	22.0	37.8	14.4	–8.8	–19.1
n	0.36	0.22	0.00	23.8	25.8	12.0	21.5	24.1	9.8	23.4	26.2	10.5	28.2	30.1	13.9	2.2	–6.3	–14.1
Product	**4**	**6**	**8**	**4**	**6**	**8**	**4**	**6**	**8**	**4**	**6**	**8**	**4**	**6**	**8**	**4**	**6**	**8**
a	1.03	1.01	*0.00*	44.8	27.4	*47.2*	43.4	27.4	*46.9*	44.4	29.4	*46.4*	49.4	32.1	*48.0*	11.3	2.0	n/a[a]
b	1.02	1.01	*0.00*	42.9	24.6	*52.7*	42.0	24.8	*52.6*	43.2	26.9	*51.9*	47.5	29.8	*52.5*	7.3	0.1	n/a[a]
c	1.02	1.01	*0.00*	38.5	20.0	*46.7*	37.8	20.3	*46.5*	39.4	22.7	*46.1*	42.6	24.4	*47.3*	30.5	0.1	n/a[a]
d	0.98	0.54	0.00	30.9	3.3	28.7	30.0	3.6	29.3	32.6	6.9	33.1	36.0	8.4	35.5	5.9	4.1	–14.3
e	1.02	1.01	*0.00*	31.8	20.5	*12.1*	29.6	19.9	*11.3*	31.2	22.4	*10.9*	36.8	25.8	*14.0*	11.2	–3.1	n/a[a]
f	1.02	1.01	0.00	34.9	10.2	37.1	33.8	10.4	37.0	35.3	12.3	39.6	39.2	15.3	43.1	4.1	–3.4	–14.2
g	1.02	1.01	*0.00*	30.7	15.2	*29.0*	29.9	15.4	*29.3*	31.7	17.8	*29.5*	33.9	21.7	*30.8*	2.8	–5.2	n/a[a]
h	*0.00*	1.01	*0.00*	*–13.1*	32.0	*26.5*	*–13.1*	31.1	*26.2*	*–12.5*	33.4	*26.3*	*–11.8*	36.4	*28.0*	n/a[a]	–3.8	n/a[a]
I	*0.00*	1.01	*0.00*	*–10.6*	30.5	*26.7*	*–10.5*	30.0	*26.7*	*–10.7*	32.1	*25.8*	*–9.8*	34.6	*27.9*	n/a[a]	–3.7	n/a[a]
j	*0.00*	0.84	*0.00*	*4.4*	31.6	*41.9*	*4.7*	31.1	*41.7*	*5.6*	33.6	*42.1*	*6.2*	35.8	*44.2*	n/a[a]	–2.9	n/a[a]

k	0.00	0.00	0.00	12.5	–9.1	19.5	12.6	–7.9	20.5	14.1	–5.5	23.2	11.7	–8.4	22.0	15.0	9.9	–6.6
l	*0.00*	*0.00*	*0.00*	*–22.0*	*19.7*	*22.0*	*–21.6*	*19.3*	*22.3*	*–21.1*	*20.0*	*22.0*	*–22.3*	*20.7*	*22.1*	n/a[a]	n/a[a]	n/a[a]
m	1.02	1.01	0.00	21.2	–0.6	32.0	20.4	–0.3	31.7	22.6	2.6	34.8	25.9	5.1	38.5	6.2	–5.2	–15.9
n	*0.00*	1.01	*0.00*	*–55.9*	8.4	*–3.9*	*–55.2*	7.7	*–3.9*	*–54.1*	10.3	*–3.4*	*–53.1*	14.2	*–0.2*	n/a[a]	–6.0	n/a[a]

[a]Unaccounted NICS values for products without ring formation due to either the C^3–X or C^5–X cleavages; this also indicates that their corresponding TSs lead to acyclic products (**9**, **10**, and **11**), whose energies and <S2> are listed *italically*.

CHAPTER 4

THERMAL REARRANGEMENTS OF HETEROATOM-BRIDGED DIALLENES [3]

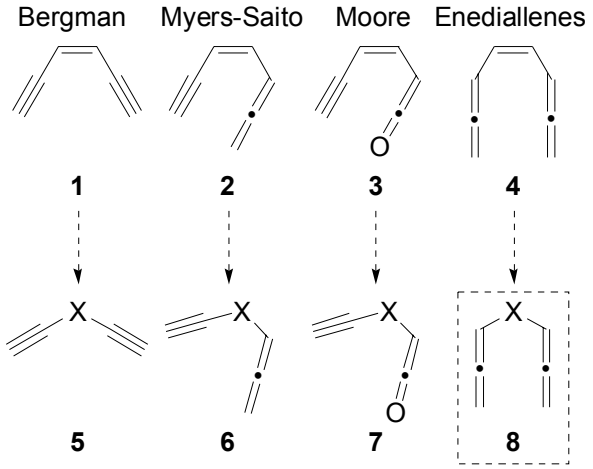
[3]Binh H. Bui and Peter R. Schreiner. The following article was submitted to *Eur. J. Org. Chem.* The VCH-RIGHTS-and-LICENCES grants permission to students to include in their theses and dissertations their own articles, or portions thereof, with expectation of due credit given to the original source.

4.1 ABSTRACT

A systematic application of the BLYP/6-311+G*//BLYP/6-31G* computational scheme was utilized to identify the favored *aromatic* 2,6-reactions leading to the formally aromatic hetero-3,4-dimethylencecyclopentadiene-di-yl from the thermal rearrangements of (hetero)atom-bridged diallenes (**X** = CH^-, NH, O, and S). Protonation of the heteroatom substituents raises the respective 2,6-cyclization barriers and the alternative 1,6-cyclizations forming the hetero-cyclohexadiene-di-yl can compete.

4.2 INTRODUCTION

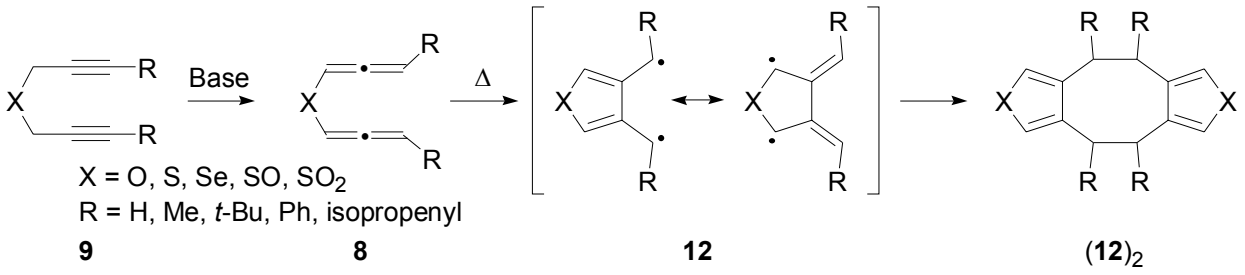
Under the umbrella of the Cope rearrangement cyclizations of polyunsaturated systems such as enediynes,[1, 2] enyne-allenes,[3, 4, 5] and enyne-ketenes,[6] have been grouped within larger "families of reactions"[7, 8, 9] for their systematization interpretation of similar reactions. The corresponding Bergman, Myers-Saito, and Moore reactions are analogous to the Cope reaction, in the sense that there is formation of a new σ-bond across the π-bonds. However, some of them



Scheme 4.1

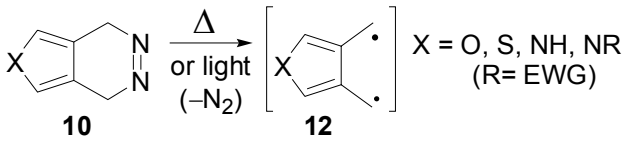
also involve an π-electron sextet that favors a reaction path leading to biradical intermediates stabilized by aromaticity. The formation of these π-electron sextets in the products or intermediates strongly affects the reaction barriers and energies. However, NICS[10] results on

the Bergman and Myers-Saito reactions indicate that aromaticity is not developed to the full in the transition structures.[9] Examining these reactions we also systematically search for new cyclization reactions. For instance, we studied heterosubstitued systems that include lone-pair carrying heteroatoms in place of the central olefinic bonds of **1**, **2**, **3**, and **4** (Scheme 4.1), i.e., **5**, **6**, **7**,[11, 12, 13] and **8**. Although experimental studies are available for the reactions of **8**,[14, 15, 16, 17, 18, 19, 20, 21] the present paper reports the necessary validation (as seen later) and computational analysis of other viable cyclization modes and delivers another building block for a new "reaction family," namely the heterosubstitued diallenic hydrocarbons.



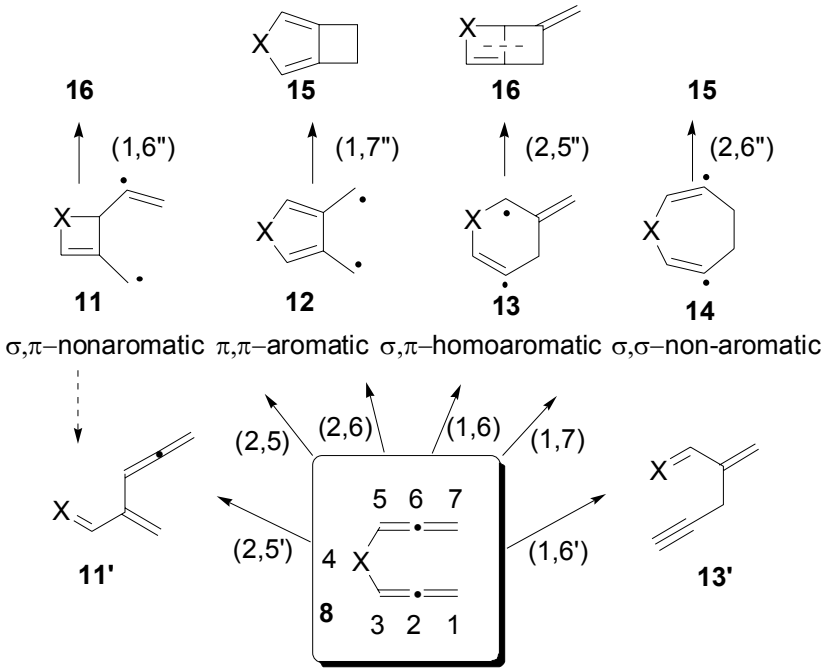
Scheme 4.2

Structures of type **8** are readily accessible through base-induced rearrangements[14, 18, 19] of the propargylic precursor **9** (Scheme 4.2). Subsequent cycloaromatizations of **8** were proposed to yield the five-membered biradical intermediate **12** (Scheme 4.2).[14] The existence of the singlet biradical **12** has been inferred by experimental studies through trapping with electron-deficient alkenes as well as with oxygen and also by a kinetic analysis of these heteroatom-bridged diallene rearrangements.[14, 19, 21] Diradical **12** was generated and observed by an alternative route.[21] Although its singlet and triplet states must be close in energy, the absence of a CIDNP effect in the NMR spectra during the cyclization of **8** indicated that the cyclizations occur on the singlet manifold.[21]



Scheme 4.3

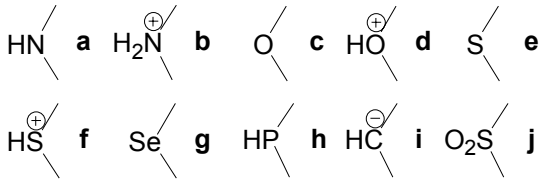
Biradical **12** belongs to the class of non-Kekulé molecules[22] characterized by the contribution of the lone pair of a heteroatom **X** to the π-conjugated hydrocarbon framework; also, **12** possesses a small singlet-triplet energy separation (ΔE_{ST}). Upon irradiation of some precursor diazenes (Scheme 4.3), Berson et al.[23, 24] generated the hetero-biradical **12** (**X** = **O**, **S**, and **NH**) for "tuning" studies of the ΔE_{ST} gaps of these molecules.[22, 25, 26] Considering the heteroatom as a bridge connecting the two termini of the biradical tetramethyleneethane (TME), they found that it is possible to adjust the ΔE_{ST} by means of the variable character of the heteroatom lone pair p_z-orbital acting on the non-bonding frontier π-orbitals (NBMOs) of TME.[25] Thus, the nature of the **X** heteroatom offers a tuning mechanism to control the molecular total electronic spin and the ΔE_{ST}.



Scheme 4.4

Apart from the 2,6-cyclizations of **8** heteroatom-bridged diallenes have not been examined with respect to other cyclization modes, i.e., through $\mathbf{TS_{25}}$, $\mathbf{TS_{16}}$, and $\mathbf{TS_{17}}$ (Scheme 4.4). On the basis of our previous computational studies,[11, 12] the 1,6-cyclization should be viable and competitive with the 2,6-reaction path. The present work provides insights into the various reaction possibilities and the importance of the **X** heteroatom on the cyclizations. While

the 2,6-cyclization product **12** demands **X** to be a π-donor to complete the aromatic π-electron sextet, the corresponding $\mathbf{TS_{26}}$ requires **X** to be a σ-acceptor because of its [2 + 2] addition nature in the early stages of the reaction coordinate.[27, 28, 29] The systematic selection of **X** with respect to the aforementioned criteria is depicted in Scheme 4.5, and we present the cyclizations of **8** to the formally aromatic hetero-3,4-dimethylenecyclopentadiene-di-yl **12**, the homoaromatic hetero-cyclohexadiene-di-yl **13**, the nonaromatic cyclobutene derivative **11**, and the cycloheptadine-di-yl **14** (Scheme 4.4). Other rearrangements of **8** leading to acyclic products such as 2-methylene-penta-3,4-dienes **11'** and 2-methylene-pent-4-ynes **13'** were considered as well.



Scheme 4.5. Selection of **X** groups for the cyclization reactions of **8**.

4.3 METHODS

All structures were optimized at DFT as implemented in the Gaussian03 package[30] using Becke's pure gradient-corrected exchange functional in conjunction with the Lee-Yang-Parr non-local correlation functional[31] (BLYP) and the 6-31G* basis set. Open-shell single state transition structures (TSs) and products were treated with an unrestricted broken-spin approach (BS-UBLYP). Analytical vibrational frequencies were computed by using second derivative computations to obtain the thermal and ZPVE corrections, and also to identify the minima and TSs. Intrinsic reaction coordinate[32] (IRC) computations were utilized to confirm the TSs. Single-point energies using the same functional but with a larger basis set (6-311+G*) were computed for all species; Brueckner doubles coupled-cluster energies[33, 34] utilizing a cc-pVDZ basis set [BD(T)/cc-pVDZ] were additionally computed for comparison in some critical cases. The validity of the computational schemes to these types of molecules has been demonstrated in our previous studies that were confirmed by other groups.[9, 29, 35, 36, 37, 38, 39, 40] NICS values[10] were computed at the geometric ring centers to assess the aromaticity of all cyclic structures.

4.4 RESULTS AND DISCUSSION

Scheme 4.4 describes the reaction paths (through $\mathbf{TS_{xy}}$) of **8** as a function of **X** leading to products **11–14**, along with competing rearrangements ($\mathbf{TS_{25'}}$ and $\mathbf{TS_{16'}}$) that result in the acyclic products **11'** and **13'**. Domino cyclizations (**TSxy"**) of **11–14** give rise to bicyclic products **15** and **16**. Although all depicted reactions were computed, we focus our discussion on the most feasible and competitive reaction pathways, i.e., $\mathbf{TS_{26}}$, $\mathbf{TS_{16}}$, and $\mathbf{TS_{17"}}$, and their respective products **12, 13,** and **15**. Relative Gibbs free activation and reaction energies as a function of **X** are presented in Figure 4.1 (a) and (b). Table 4.1 provides relative energies at BLYP/6-311+G**//BLYP/6-31G* + ZPVE as well as the NICS values for all cyclic species.

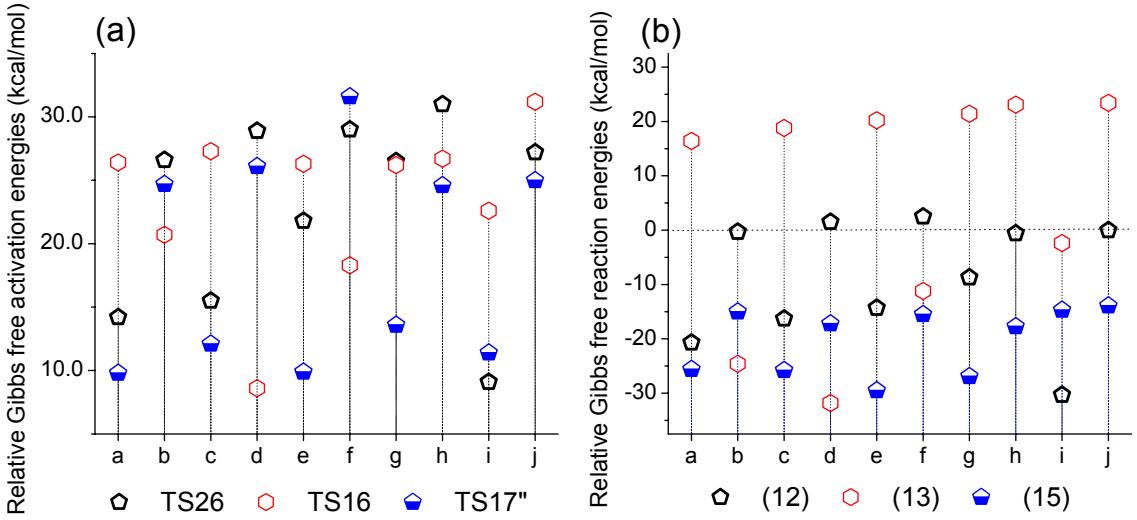
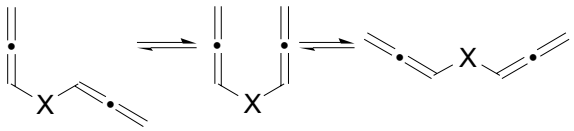


Figure 4.1. (**a**) Relative Gibbs free activation energies (kcal mol^{-1}, 298 K, at UBLYP/6-31G*) for the thermal cyclizations of **8** as a function of **X** to form **12**, **13** (***13d', 13f'***), and **15**; (**b**) Relative Gibbs free reaction energies (kcal mol^{-1}, 298 K, at UBLYP/6-31G*) for the thermal cyclizations of **8** as a function of **X** to form **12**, **13** (***13d', 13f'***), and **15**.

The two-fold base-catalyzed propargyl-allene isomerization of **9** (Scheme 4.2) yields the diallenes **8** that displays three conformers (Scheme 4.6). Their energy differences depending on

X are in the range of 0.2–8.8 kcal mol^{-1} mostly in favor of **8c** (for **X** = **a**, **b**, **g**, **i** and **j**) then **8a** (for **X** = **c**, **d**, and **e**). The ΔG and $\Delta G^{\ddagger}$ were computed with respect to the global minimum of the conformers**,** i.e., **8a**, **8b**, or **8c**, depending on the nature of **X**.



8a **8b** **8c**

Scheme 4.6

Diallenes **8** rearrange to **12**[21] through a [2+2]-bond formation across the central allene carbon atoms; the absence of a kinetic isotope effect signals little or no rotation of the terminal methylene units in the **TS**.[19] This suggests an early transition structure for this exothermic reaction, which is confirmed by the computed negative ΔG (**12**) except for **X** = **d** and **f** (Figure 4.1 (b)).

The experimental activation barriers (E_a) for the cyclization associated with $\mathbf{TS}_{26}$ are 14.3±1.7, 22.0±2.4, and 34.2±3.6 kcal mol^{-1} for **X** = **e**, **c**, and **j**.[21] It was rationalized that the increase in the observed activation energies corresponds to a decrease in aromatic stabilization in the respective products **12**.[21] The lone pairs of **X** completing the π-electron sextet govern the reaction barriers. However, the computed $\Delta G^{\ddagger}$ ($\mathbf{TS_{26}}$) values are 21.8, 15.5, and 27.2 kcal mol^{-1} for **X** = **e**, **c**, and **j**, respectively. Obviously, our calculation shows a different order of the activation energies, i.e., $\Delta G^{\ddagger}$ $\mathbf{TS_{26}c}$ < $\Delta G^{\ddagger}$ $\mathbf{TS_{26}e}$ < $\Delta G^{\ddagger}$ $\mathbf{TS_{26}j}$, which is supported by the computed thermodynamic stabilization order of ΔG (**12c**) < ΔG (**12e**) < ΔG (**12j**). Previous computational studies[11, 12, 13] on the cycloaromatizations of **5, 6,** and **7** to the formally aromatic five-membered rings resulted in a similar computational trend (for **X** = **c** and **e**). Thus, it is questionable if the lone pair contribution of the sulfur instead of oxygen favors the aromatic stabilization. Further, from studies on the anomeric effect and hyperconjugation Salzner and Schleyer concluded that the orbital interactions with the lone pair of sulfur or higher row atoms of the same group are less effective than those of oxygen.[41]

Figure 4.2 displays the linear correlation we found for the $\Delta G^{\ddagger}$ ($\mathbf{TS_{26}}$) and corresponding ΔG (**12**); this correlation supports the notion of an aromatic π-electron sextet stabilizing the products. As **X**'s ability to donate the lone pair of electrons[42] to the π-electron system

decreases in the order of **X** (**i**, **a**, **c**, **e**, **g**, **j**, **h)**, the activation barriers increase similarly. Note that the exergonicities also decrease proportionally to the decreasing electron-donating ability of **X**.

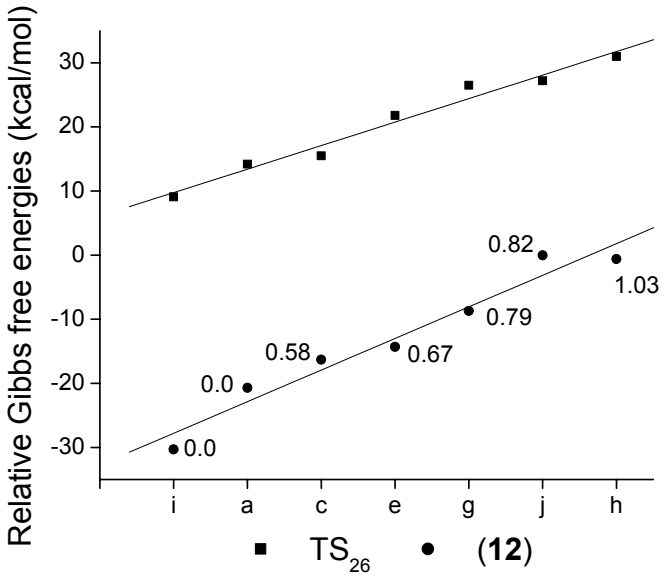


Figure 4.2. Relative Gibbs free activation (squares) of the **TS_{26}** and reaction energies (dots) of products **12** computed at UBLYP/6-31G*. The expectation values of the Slater determinants (<S^2>) are listed next to energetic data points but not for those points of **TS_{26}** whose <S^2> values are equal to zero.

The computed NICS values (Table 4.1) provide a finer interpretation of the plots in Figure 4.2. While all NICS values of the products are rather small, those of the transition structures are large. Hence, aromaticity is a key factor for the transition structures but not for the products, at least according to the NICS analysis. Oddly, there seems to be a direct relationship between the magnitude of the barrier and the NICS value: high barriers have large negative NICS values. Hence, while delocalization is clearly important from a structural viewpoint, the initial [2+2] approach during the ring closure[27, 28] is more important for the barrier heights than cyclic delocalization. Rotations of the two methylene groups occur later on the reaction path (Figure 4.3) and result in the conjugation of their two lone pair p_z-orbitals with the molecular π-system; this greatly diminishes the cyclic π-delocalization in the products. As a consequence of this analysis we conclude that bis-allyl stabilization is the most important contribution to the relative ease of generating products **12**.

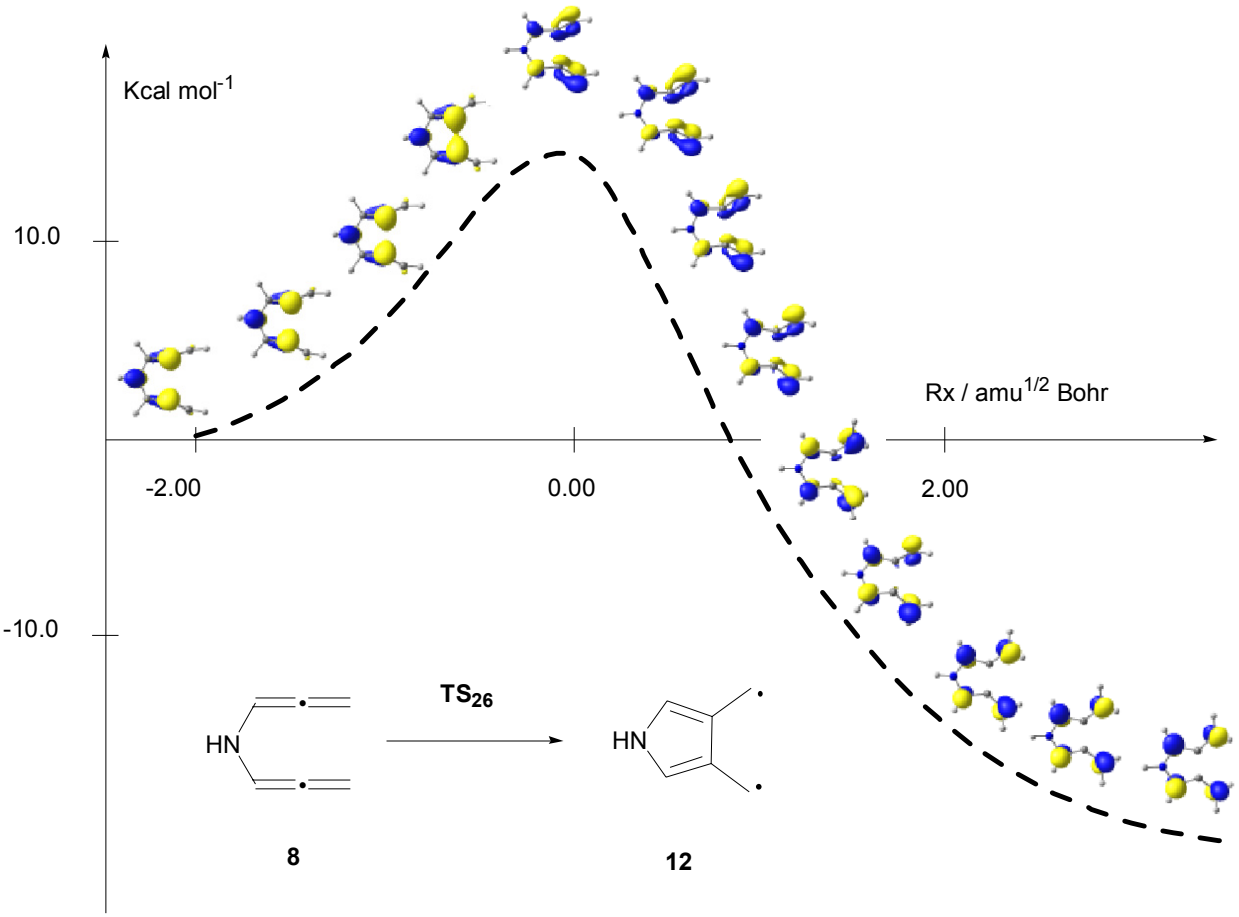


Figure 4.3. Transformation of the HOMO along the reaction path of the 2,6-cyclization of **8** to form **12** with **X =** NH.

The analyses of the frontier molecular orbitals of $\mathbf{TS_{26}}$ and the product for **X** = NH confirm the notion of an early electronic development in the transition structure (Figure 4.4). Early in the reaction path (Figure 4.3), little or no rotation of the terminal methylene groups is observed.[21] Note that the increasing overlap of the HOMO of the starting materials lowers its energies as the reaction progresses towards the transition structure. In the transition structure, the former HOMO has become HOMO–1 and the character of the new HOMO no longer describes the σ-bond formation. Instead, the π-HOMO takes over and determines the second half of the reaction path. Transformation of the in-plane π-orbitals into the σ-orbitals (TS's HOMO) requires the reactant **8** to assume the proper conformation (**8b**, Scheme 4.5). The antibonding character of the HOMO is too small to result in significant σ-π-mixing MO across

the C–C bond formation. Hence, the character of the reaction path changes from σ-bond formation to π-space interaction shortly before the transition structure.

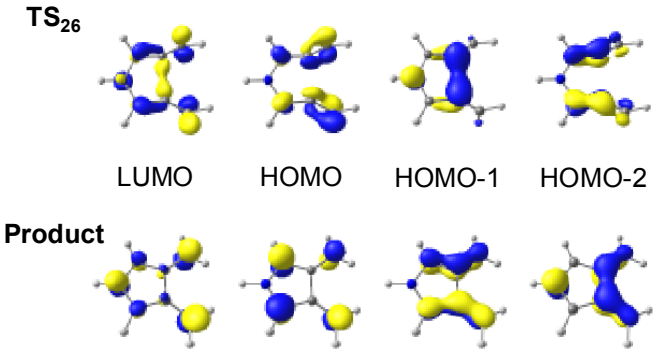


Figure 4.4. Frontier molecular orbitals of the transition structure and product of the 2,6-cyclization of **8** to form **12** with **X =** NH.

The electronic perturbation through the heteroatom in product **12** and **TS$_{26}$** can be analyzed with the help of the FMOs (Figure 4.4). For **X** = **i**, **a**, **c**, **e**, **g**, **j**, **h**, the available electron lone pair interacts with the molecular π-system to complete the π-electron sextet (HOMO-2). The strong perturbation of the **X**-heteroatom lowers the activation barrier (Figure 4.2), increases the HOMO and LUMO energy separation, and brings about the singlet nature of the products.[25] Vice versa, when the donor ability of **X** diminishes, the HOMO and LUMO of the products approach the degeneracy allowing singlet-triplet (S–T) mixing (Figure 4.2).

The contribution of the electron lone pair of **X** can be turned off by protonation (**X** = **b**, **d**, and **f** versus **a**, **c**, and **e**) and the $\Delta G^{\ddagger}$ (**TS$_{26}$**) increase accordingly by 7.2–13.4 kcal mol^{-1}. The computed NICS values of **TS$_{26}$** (**X** = **b**, **d**, and **f**) are smaller than those of **TS$_{26}$** (**X** = **a**, **c**, and **e**, Table 4.1) indicating the loss of cyclic delocalization due to protonation of the **X** substituents. The Gibbs reaction energies for protonated **12b**, **12d**, and **12f** are less exergonic than those of the non-protonated **12a**, **12c**, and **12e** (Figure 4.1), resulting from the inability to form an aromatic π-electron sextet.

Consequently, the homoaromatic 1,6-reaction of **8** forming **13** becomes more favorable relative to the 2,6-cyclization upon protonation of the **X** heteroatom; Figure 4.1 indicates that the **TS$_{16}$** barriers are lower than those of **TS$_{26}$** for **X** = **b**, **d**, and **f**. The reaction path **TS$_{16}$** also competes with **TS$_{26}$** in the cases of non-protonated **X** substituents such as **g** and **h**. However, the

thermodynamic stabilizations are in favor of all studied five-membered cyclic products **12** instead of the six-membered ring products **13**; most ΔG (**13**) values are highly endergonic except for **13b and 13i** (–24.6 and –2.4, respectively). Further, the ΔG values of –31.8 and –11.2 kcal mol^{-1} correspond to structures **13d'** and **13f'** resulting from the Claisen-like rearrangement (**TS$_{16'}$**) to form the more stable acyclic products **13'** (Scheme 4.4).

Table 4.1. Relative single point energies (kcal mol^{-1}), and NICS values (for only the 5-, and 6-membered ring compounds) at BLYP/6-311+G*//BLYP/6-31G* + ZPVE for the TSs and products of the thermal cyclization of the heteroatom-bridged diallenes (**8**).

	BLYP/ 6-311+G*//BLYP/6-31G* +ZPVE						
X	**<S^2>**		**ΔE**			**NICS**	
	TS$_{26}$	**TS$_{16}$**	**TS$_{26}$**	**TS$_{16}$**	**TS$_{17''}$**[b]	**TS$_{26}$**	**TS$_{16}$**
a	0.00	0.00	13.9	25.3	10.0	–11.2	–11.1
b	0.00	0.00	26.5	19.3	25.5	–4.3	–18.8
c	0.00	0.00	15.7	26.1	12.4	–10.1	–11.5
d	0.00	0.00	28.9	7.1	26.9	–5.6	–11.4
e	0.00	0.00	21.5	25.2	9.5	–12.1	–19.5
f	0.00	0.00	28.5	16.7	31.2	–6.7	–20.0
g	0.00	0.00	24.5	23.3	11.5	–11.5	–19.8
h	0.00	0.00	30.9	25.3	24.6	–1.3	–20.2
i	0.00	0.00	5.5	17.6	10.0	–8.6	–8.2
j	0.00	0.00	27.0	29.6	25.9	–3.9	–15.6
	12	**13**	**12**	**13**	**15**	**12**	**13**
a	0.00	0.00	–19.9	15.1	–23.7	2.2	–1.1
b	1.01	0.00	1.0	–25.2	–13.4	–2.7	–2.5
c	0.58	0.70	–14.7	18.8	–24.1	0.1	–2.2
d	1.04	0.00	3.2	*–33.5*	–15.3	–4.1	n/a[a]
e	0.67	0.92	–13.9	20.5	–27.8	3.4	–2.6
f	0.97	0.00	3.8	*–12.5*	–14.2	–3.2	n/a[a]
g	0.79	0.82	–9.6	19.7	–27.1	5.3	–3.0
h	1.04	0.75	0.9	23.0	–15.5	–0.5	–3.6
i	0.00	0.00	–31.5	–7.8	–14.8	7.0	4.1
j	0.82	1.02	1.2	25.0	–12.2	–1.9	–2.3

[a]Unaccounted NICS values for products without ring formation due to either the C^3–**X** or C^5–**X** cleavages; this also indicates that their corresponding TSs lead to acyclic products (**13'**), whose energies are listed in *italics*.
[b]The actual barriers for these domino cyclizations must be relative to structures **12** instead of the reactants (**8**).

Although the 2,6-cycloaromatizations of **8** exergonically form the five-membered cyclic products **12**, subsequent cyclizations (**TS$_{17''}$**) of **12** to yield the bicyclic products **15** are

improbable. This is due to the high activation barrier (ΔG (**TS17"**) = 22–42 kcal mol^{-1}, relative to structures (**12**), and the expected short lifetime of the biradical products **12**. Berson et al. reported the formation of **15** from **12** (**X** = **O** and **S**) only in low yields at high temperature conditions using flash vacuum pyrolysis.[24] Instead, biradicals **12** typically dimerize at their methylene units (Scheme 4.2).[21]

4.5 CONCLUSIONS

By means of systematic computational comparisons of the cyclizations and rearrangements of heteroatom-bridged diallenes **8** we find that *aromatization* reactions (**TS_{26}**) are preferred and lead to the formally aromatic hetero-3,4-dimethylencecyclopentadiene-di-yl **12**. The ability of the heteroatom (or group) **X** to contribute π-electron to the π-electron aromatic sextet governs the barriers (**TS_{26}**) but not the reaction energies. As a consequence, protonation of the **X** heteroatom disrupts the aromatic sextets and results in an increase of ΔG and $\Delta G^{\ddagger}$, and gives way to the competing 1,6-reaction paths.

4.6 ACKNOWLEDGMENTS

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4.7 REFERENCES

[1] Jones, R. R.; Bergman, R. G., *J. Am. Chem. Soc.* **1972**, *94*, 660.

[2] Lockhart, T. P.; Comita, P. B.; Bergman, R. G., *J. Am. Chem. Soc.* **1981**, *103*, 4082.

[3] Myers, A. G.; Kuo, E. Y.; Finney, N. S., *J. Am. Chem. Soc.* **1989**, *111*, 8057.

[4] Nagata, R.; Yamanaka, H.; Okazaki, E.; Saito, I., *Tetrahedron Lett.* **1989**, *30*, 4995.

[5] Schmittel, M.; Kiau, S.; Siebert, T.; Strittmatter, M., *Tetrahedron Lett.* **1996**, *37(43)*, 7691.

[6] Foland, L. D.; Karlsson, J. O.; Perri, S. T.; Schwabe, R.; Xu, S. L.; Patil, S.; Moore, H. W., *J. Am. Chem. Soc* **1989**, *111*, 975.

[7] Hopf, H., (2000) *Classics in Hydrocarbon Chemistry*. Weinheim: Wiley-VCH.

[8] Navarro-Vazquez, A.; Prall, M.; Schreiner, P. R., *Org. Lett.* **2004**, *6*, 2981.

[9] Schreiner, P. R.; Navarro-Vázquez, A.; Prall, M., *Acc. Chem. Res.* **2005**, *38*, 29.

[10] Schleyer, P. v. R.; Maerker, C.; Dransfeld, A.; Jiao, H. J.; Hommes, N., *J. Am. Chem. Soc.* **1996**, *118*, 6317.

[11] Bui, B. H.; Schreiner, P. R., *Org. Lett.* **2003**, *5*, 4871.

[12] Bui, B. H.; Schreiner, P. R., *Eur. J. Org. Chem.* **2006**, *2006*, 1162.

[13] Kawatkar, S. P.; Schreiner, P. R., *Org. Lett.* **2002**, *4*, 3643.

[14] Braverman, S.; Zafrani, Y.; Gottlieb, H. E., *Tetrahedron Lett.* **2000**, *41*, 2675.

[15] Braverman, S.; Zafrani, Y.; Gottlieb, H. E., *Tetrahedron* **2001**, *57*, 9177.

[16] Zafrani, Y.; Cherkinsky, M.; Gottlieb, H. E.; Braverman, S., *Tetrahedron* **2003**, *59*, 2641.

[17] Arino, P.; Camps, F.; Serratosa, F., *An. Quim.* **1970**, *66*, 995.

[18] Braverman, S.; Duar, Y.; Segev, D., *Tetrahedron Lett.* **1976**, 3181.

[19] Braverman, S.; Duar, Y., *J. Am. Chem. Soc.* **1990**, *112*, 5830.

[20] Cheng, Y. S. P.; Dominguez, E.; Garratt, P. J.; Neoh, S. B., *Tetrahedron Lett.* **1978**, 691.

[21] Cheng, Y. S. P.; Garratt, P. J.; Neoh, S. B.; Rumjanek, V. M., *Isr. J. Chem.* **1985**, *26*, 101.

[22] Berson, J. A., *Acc. Chem. Res.* **1997**, *30*, 238.

[23] Greenberg, M. M.; Blackstock, S. C.; Berson, J. A.; Merrill, R. A.; Duchamp, J. C.; Zilm, K. W., *J. Am. Chem. Soc.* **1991**, *113*, 2318.

[24] Stone, K. J.; Greenberg, M. M.; Blackstock, S. C.; Berson, J. A., *J. Am. Chem. Soc.* **1989**, *111*, 3659.

[25] Bush, L. C.; Heath, R. B.; Feng, X. W.; Wang, P. A.; Maksimovic, L.; Song, A. I.; Chung, W. S.; Berinstain, A. B.; Scaiano, J. C.; Berson, J. A., *J. Am. Chem. Soc.* **1997**, *119*, 1406.

[26] Berson, J. A., *J. Mol. Struct. (Theochem)* **1998**, *424*, 21.

[27] Alabugin, I. V.; Manoharan, M., *J. Phys. Chem. A* **2003**, *107*, 3363.

[28] Alabugin, I. V.; Manoharan, M.; Kovalenko, S. V., *Org. Lett.* **2002**, *4*, 1119.

[29] Prall, M.; Wittkopp, A.; Schreiner, P. R., *J. Phys. Chem.* **2001**, *105*, 9265.

[30] Frisch, M. J.; Trucks, G. W.; H. B. Schlegel; G. E. Scuseria; M. A. Robb; J. R. Cheeseman; J. A. Montgomery; Jr., T. V.; K. N. Kudin; J. C. Burant; J. M. Millam; S. S. Iyengar; J. Tomasi; V. Barone; B. Mennucci; M. Cossi; G. Scalmani; N. Rega; G. A. Petersson; H. Nakatsuji; M. Hada; M. Ehara; K. Toyota; R. Fukuda; J. Hasegawa; M. Ishida; T. Nakajima; Y. Honda; O. Kitao; H. Nakai; M. Klene; X. Li; J. E. Knox; H. P. Hratchian; J. B. Cross; C. Adamo; J. Jaramillo; R. Gomperts; R. E. Stratmann; O. Yazyev; A. J. Austin; R. Cammi; C. Pomelli; J. W. Ochterski; P. Y. Ayala; K. Morokuma; G. A. Voth; P. Salvador; J. J. Dannenberg; V. G. Zakrzewski; S. Dapprich; A. D. Daniels; M. C. Strain; O. Farkas; D. K. Malick; A. D. Rabuck; K. Raghavachari; J. B. Foresman; J. V. Ortiz; Q. Cui; A. G. Baboul; S. Clifford; J. Cioslowski; B. B. Stefanov; G. Liu; A. Liashenko; P. Piskorz; I. Komaromi; R. L. Martin; D. J. Fox; T. Keith; M. A. Al-Laham; C. Y. Peng; A. Nanayakkara; M. Challacombe; P. M. W. Gill; B. Johnson; W. Chen; M. W. Wong; C. Gonzalez; Pople, J. A. *GAUSSIAN 03, REVISION B.03*, Gaussian, Inc.: Pittsburgh PA, 2003.

[31] Becke, A. D., *Phys. Rev. A* **1988**, *38*, 3098.

[32] Gonzalez, C.; Schlegel, H. B., *J. Chem. Phys.* **1989**, *90*, 2154.

[33] Handy, N. C.; Pople, J. A.; Head-Gordon, M.; Raghavachari, K., *Chem. Phys. Lett.* **1989**, *164*, 185.

[34] Crawford, T. D.; Kraka, E.; Stanton, J. F.; Cremer, D., *J. Chem. Phys.* **2001**, *114*, 10638.

[35] Cramer, C. J., *J. Am. Chem. Soc.* **1998**, *120*, 6261.

[36] Gräfenstein, J.; Hjerpe, A. M.; Kraka, E.; Cremer, D., *J. Phys. Chem. A* **2000**, *104*, 1748.

[37] Gräfenstein, J.; Kraka, E.; Filatov, M.; Cremer, D., *Int. J. Mol. Sci.* **2002**, *3*, 360.

[38] Schreiner, P. R.; Prall, M., *J. Am. Chem. Soc* **1999**, *121*, 8615.

[39] Stahl, F.; Moran, D.; Schleyer, P. v. R.; Prall, M.; Schreiner, P. R., *J. Org. Chem.* **2002**, *67*, 1453.

[40] Wenthold, P. G.; Lipton, M. A., *J. Am. Chem. Soc* **2000**, *122*, 9265.

[41] Salzner, U.; Schleyer, P. v. R., *J. Am. Chem. Soc.* **1993**, *115*, 10231.

[42] Schleyer, P. v. R., *Pure Appl. Chem.* **1987**, *59*, 1647.

4.8 SUPPLEMENTAL MATERIAL

for

THERMAL REARRANGEMENTS OF HETEROATOM-BRIDGED DIALLENES

Binh H. Bui and Peter R. Schreiner[1]

Department of Chemistry University of Georgia, Athens, Georgia 30602-2525

[1] E-mail: prs@chem.uga.edu; prs@org.chemie.uni-giessen.de

Table 4.2. Evaluation of the contradiction between the experimental results on the TS_{26} reaction of 8 with X = O, and S (22.0 and 14.3 kcal/mol, respectively) and the calculated values of 15.5 and 21.8 kcal/mol.

	Reactant **8** (X = O)			
Conformers (scheme 6)	**b**	**a**	**c**	**TS26**
Point group:	C2v	Cs	C2v	Cs
Name of Comp. cluster	Darmstadt	Darmstadt	Darmstadt	Darmstadt
ZPE	0.095103	0.095085	0.094623	0.094583
Eo=Eelec+ZPE	–307.110872	–307.112632	–307.110256	–307.091009
Thermal E	–307.102913	–307.104634	–307.102053	–307.084276
H = E+RT	–307.101969	–307.10369	–307.101109	–307.083331
G = H -TS	**–307.143142**	**–307.146165**	**–307.14306**	**–307.121399**
ΔG of Conformers	1.8970	**0.0000**	1.9484	
$\Delta G(TS_{26})$--rel. to **b, a, c**	13.6	**15.5**	13.6	
	Reactant **8** (X = S)			
Conformers (scheme 6)	**b**	**a**	**c**	**TS26**
Point group:	C2	C1	Cs	Cs
cluster	Darmstadt	Darmstadt	Darmstadt	Darmstadt
ZPE	0.091401	0.091701	0.091465	0.090897
Eo=Eelec+ZPE	–630.087353	–630.091147	–630.089837	–630.058691
Thermal E	–630.079527	–630.082601	–630.081181	–630.051262
H = E+RT	–630.078583	–630.081656	–630.080237	–630.050318
G = H –TS	**–630.119688**	**–630.125398**	**–630.124673**	**–630.09072**
ΔG of Conformers	3.5831	**0.0000**	0.4549	
$\Delta G(TS_{26})$--rel. to **b, a, c**	18.2	**21.8**	21.3	

Table 4.3. Relative energies (kcal mol^{-1}), **<S^2>** and NICS values for the TSs and products of the thermal cyclization of the heteroatom-bridged diallenes (**8**).

	BLYP/6-31G*								BLYP/ 6-311+G*// BLYP/6-31G*				
X	**<S^2>**		**ΔH**			**ΔG**			**ΔE (+ZPVE)**			**NICS**	
	TS$_{26}$	**TS$_{16}$**	**TS$_{26}$**	**TS$_{16}$**	**TS$_{17''}$**[b]	**TS$_{26}$**	**TS$_{16}$**	**TS$_{17''}$**[b]	**TS$_{26}$**	**TS$_{16}$**	**TS$_{17''}$**[b]	**TS$_{26}$**	**TS$_{16}$**
a	0.00	0.00	11.7	23.5	5.6	14.2	26.4	9.8	13.9	25.3	10.0	–11.2	–11.1
b	0.00	0.00	23.9	19.4	21.1	26.6	20.7	24.7	26.5	19.3	25.5	–4.3	–18.8
c	0.00	0.00	12.8	24.5	7.9	15.5	27.3	12.1	15.7	26.1	12.4	–10.1	–11.5
d	0.00	0.00	26.3	7.9	22.7	28.9	8.6	26.1	28.9	7.1	26.9	–5.6	–11.4
e	0.00	0.00	19.7	24.1	5.6	21.8	26.3	9.9	21.5	25.2	9.5	–12.1	–19.5
f	0.00	0.00	26.1	16.8	28.1	29.0	18.3	31.6	28.5	16.7	31.2	–6.7	–20.0
g	0.00	0.00	23.0	22.6	8.0	26.5	26.2	13.6	24.5	23.3	11.5	–11.5	–19.8
h	0.00	0.00	28.0	23.7	20.6	31.0	26.7	24.6	30.9	25.3	24.6	–1.3	–20.2
i	0.00	0.00	6.4	19.1	6.3	9.1	22.6	11.4	5.5	17.6	10.0	–8.6	–8.2
j	0.00	0.00	24.8	28.9	21.8	27.2	31.2	25.0	27.0	29.6	25.9	–3.9	–15.6
	12	**13**	**12**	**13**	**15**	**12**	**13**	**15**	**12**	**13**	**15**	**12**	**13**
a	0.00	0.00	–24.2	13.1	–30.2	–20.7	16.4	–25.6	–19.9	15.1	–23.7	2.2	–1.1
b	1.01	0.00	–3.6	–25.9	–19.4	–0.3	–24.6	–15.0	1.0	–25.2	–13.4	–2.7	–2.5
c	0.58	0.70	–19.5	15.8	–30.7	–16.3	18.8	–25.8	–14.7	18.8	–24.1	0.1	–2.2
d	1.04	0.00	–1.5	–32.9	–21.4	1.5	–31.8	–17.2	3.2	*–33.5*	–15.3	–4.1	n/a[a]
e	0.67	0.92	–18.0	17.7	–34.3	–14.3	20.2	–29.5	–13.9	20.5	–27.8	3.4	–2.6
f	0.97	0.00	–0.7	–12.4	–19.7	2.5	–11.2	–15.5	3.8	*–12.5*	–14.2	–3.2	n/a[a]
g	0.79	0.82	–13.7	17.9	–33.1	–8.7	21.4	–26.9	–9.6	19.7	–27.1	5.3	–3.0
h	1.04	0.75	–4.1	19.9	–22.3	–0.6	23.1	–17.7	0.9	23.0	–15.5	–0.5	–3.6
i	0.00	0.00	–34.4	–6.6	–19.9	–30.3	–2.4	–14.7	–31.5	–7.8	–14.8	7.0	4.1
j	0.82	1.02	–3.5	21.6	–18.2	–0.03	23.4	–13.9	1.2	25.0	–12.2	–1.9	–2.3

[a]Unaccounted NICS values for products without ring formation due to either the C^3–**X** or C^5–**X** cleavages; this also indicates that their corresponding TSs lead to acyclic products (**13'**), whose energies are listed in *italics*.
[b]The actual barriers for these domino cyclizations must be relative to structures **12** instead of the reactants (**8**)

CHAPTER 5

SUMMARY AND CONCLUDING REMARKS

By means of systematic strategies, i.e., classification and methodological applications of available computational tools, I have examined various cyclizations of heterosubstituted polyunsaturated hydrocarbons. This "*heuristic chemistry*" approach enables quick qualitative predictions of new chemical systems involving novel transformations. The efficacy of the unrestricted broken-symmetry DFT approach was exploited to be a practical tool to study a wide range of polyunsaturated hydrocarbon reactions that involve multiconfigurational biradical intermediates. The three projects presented here not only broadened my chemical knowledge, but strengthened my research skills that can be used for future endeavors.

In the three projects I have computed and evaluated all possible cyclization modes of the heterosubstituted polyunsaturated hydrocarbon systems, i.e., 4-heteroatom-1,2-hexadiene-5-ynes, 3-heteroatom-pent-1-en-4-yn-1-ones, and (hetero)atom-bridged diallenes. It was found that the *aromatization* 2,6-cyclization path leading to the formally aromatic five-membered ring products are preferred and experimentally accessible. The σ-electron-withdrawing and π-electron-donating abilities of the heteroatom (or group) **X** have been probed to be effective in governing the reaction barriers but not the reaction energies. The electronic perturbation through the heteroatom by protonation could results in other competitive reaction paths that are either the

1,6-cyclization mode to form the homoaromatic six-membered ring product or the 1,6-Claisen-type rearrangement to form the stable acyclic product. Hence, application of systematic strategies has proven to be a practical approach for the investigations of the aforementioned projects.