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Computational Studies on the Cyclizations of Enediynes, Enyne-Allenes, and Related Polyunsaturated Systems[†]

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ABSTRACT
Quantum chemical studies of cyclizations of enediynes and enyne-allenes have proven to be computationally tractable thanks to the success of the unrestricted broken spin symmetry (UBS) approach using GGA functionals for the description of open-shell biradicals; the results can further be improved through single-point energy coupled-cluster computations [CCSD(T), BD(T)]. This made comprehensive computational studies on substituent effects and heterosubstituted systems possible. For convenience and predicting new reactions, these transformations can be grouped within larger "families". Alternative cyclization modes are predicted and await experimental realization.

Introduction

The Bergman[1] and related reactions are of pivotal importance in organic synthesis,[2] in carbon-rich materials,[3] and especially in pharmacology since enediyne antibiotics[4] were isolated from microorganisms in the 1980s. These molecules act as natural antibiotics destroying the DNA of bacteria and viruses. They are classified into three families: the calicheamicin/esperamicin, the dynemicin, and the chromoprotein family, of which typical representatives are Calicheamicin γ^{I}_{1}, Dynemicin A, and Neocarzinostatin, respectively (Scheme 1). All of these possess the enediyne pharmacophore that is held responsible for the DNA cleavage. Whereas 10-membered ring calicheamicin and dynemicin families form a 1,4-dehydrobenzene biradical upon Bergman cyclization, enyne-allene drugs such as Neocarzinostatin, with a nine-membered ring, give a biradical intermediate through a Myers−Saito-type cyclization,[5] upon formation of a reactive cumulene form. The cytotoxicity of these molecules is based on the abstraction of hydrogens from the sugar backbone of DNA, which leads to DNA cleavage and cell death. The interest in these systems eventually led to the discovery of new reactions with DNA-cleavage capacity like the C^2-C^6 "Schmittel cyclization" of enyne-allenes (Scheme 2).[6]

The biological relevance of these reactions, along with their challenging electronic structures, called the attention of computational chemists, and many theoretical methodologies were applied to these systems. In this Account, we will try to show how computational chemistry may deal with these cyclizations, how to avoid pitfalls, and how to choose an appropriate method at reasonable computational effort. Beyond technical considerations, computational chemistry may be used to validate, interpret, and predict[7] experimental results, the latter aspect being probably the most valuable but least utilized. True predictions are difficult and require that the computational results are validated against accurate experimental numbers and that the interpretation of the collective findings is self-consistent. Helpful along this way are reactions or structures that are similar enough to allow a relatively safe interpretation and extrapolation, that is, "families of reactions." Such a "family" emerges when the above transformations are viewed within the larger framework of Cope-type reactions.[8]

To the best of our knowledge, Houk et al.,[9] as well as Hopf,[10] were the first to recognize this obvious connection that bears important consequences. Hence, within this line of thinking, Bergman,[1] Myers−Saito,[5] and many related reactions are classified in the broader scheme of Cope rearrangements. As a consequence, one may ask why there are subtle but distinct differences in these types of reactions, for instance, that it is generally accepted that while the Cope rearrangement of **9** does not involve an intermediate, it is the *p*-didehydrobenzene biradical **3** that is able to abstract hydrogens from simple (e.g., cyclohexadiene) or complex (e.g., DNA) H-donors in the cyclization of **1** (Scheme 3). When these reactions are viewed as related, one can predict the involvement of biradical intermediates. These and related aspects are discussed in the following.

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[†] This review is dedicated to Prof. Weston Thatcher Borden for his seminal contributions to theoretical organic chemistry on the occasion of his 60th birthday.

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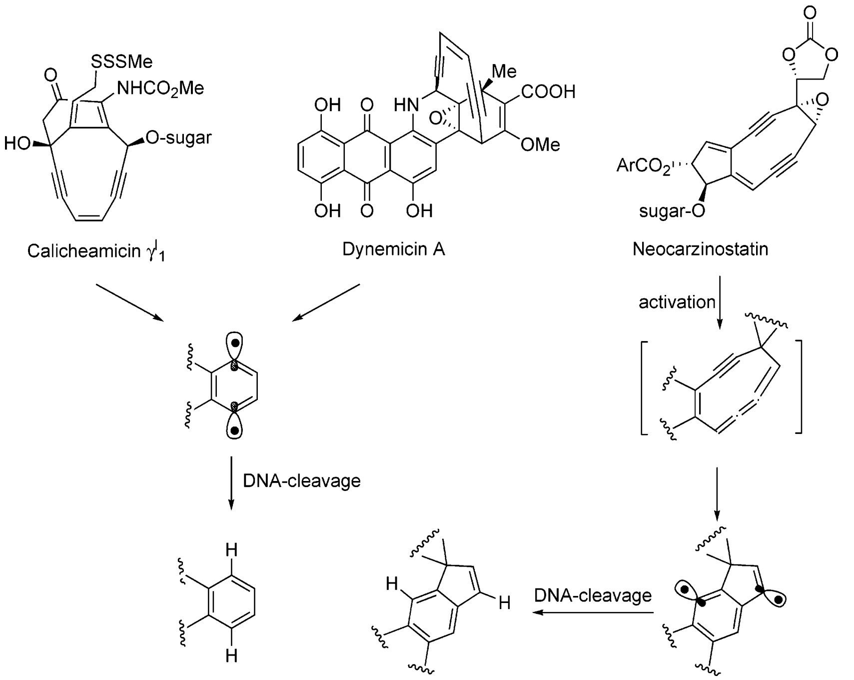
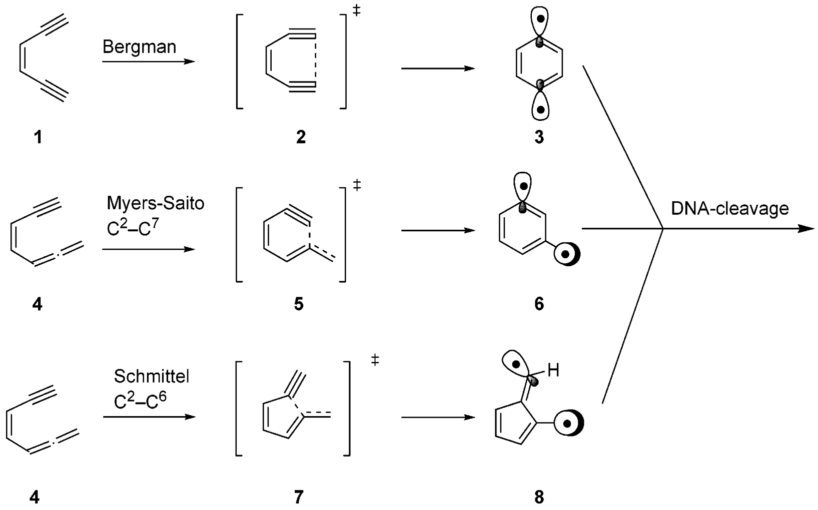
Scheme 1. Action Mode of Enediyne Antibiotics



Scheme 2. Bergman, Myers–Saito, and Schmittel Reactions

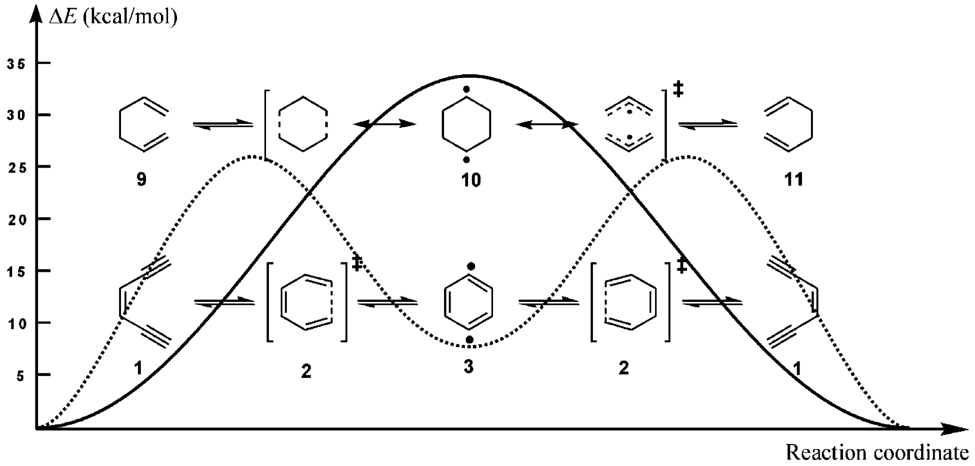


Experimental Thermochemical Data

To validate computational results accurate thermodynamic data for a representative subset of the reactions under study are required. Data for the Bergman cyclization of **1** are experimentally available through the work of Roth and co-workers,[11] who showed that the reaction is moderately endothermic ($\Delta H_{298\ \mathrm{K}} = 8.5 \pm 1.0$ kcal/mol) and associated with forward and reverse barriers of $\Delta^{\ddagger}H_{470\ \mathrm{K}}(\mathbf{1}\rightarrow\mathbf{3}) = 28.2 \pm 0.5$ and $\Delta^{\ddagger}H_{470\ \mathrm{K}}(\mathbf{3}\rightarrow\mathbf{1}) = 19.7 \pm 0.7$ kcal/mol. The singlet–triplet energy gap, $\Delta E_{\mathrm{ST},298\ \mathrm{K}}$ was determined to be 3.8 ± 0.5 kcal/mol.[12] Through DFT computation of the thermochemical data $\Delta^{\ddagger}H$, ΔH, and ΔE_{ST} were computed to be 30.1 ± 0.5, 7.8 ± 1.0, and 3.5 ± 0.5 kcal/mol, respectively.[13]

Thermochemical parameters for the Myers–Saito reaction are also available.[5b] Determination of rate constants in the range of 39–100 °C results in $\Delta^{\ddagger}H = 21.8 \pm 0.5$ and $\Delta^{\ddagger}S = -11.6 \pm 1.5$ eu, which gives $\Delta^{\ddagger}G_{298\ \mathrm{K}} = 25.3 \pm 0.5$ kcal/mol, whereas the reaction enthalpy was calculated to be $\Delta H_{298\ \mathrm{K}} = -15 \pm 3$ kcal/mol. The comparison between computed and experimental data is not straightforward in all cases. First of all, most publications give activation and reaction energies computed from the less stable reactive form *s*-cis conformer **4b**, although the *s*-trans form **4a** is nearly 4 kcal/mol more stable (Figure 1);[14] the experimentally determined thermochemical data must refer to the cyclization from the latter. We have computed a $\Delta\Delta G_{298\ \mathrm{K}}$ between the two conformers of 3.5 kcal/mol at B3LYP/6-311G**, which results in $\Delta^{\ddagger}G_{298\ \mathrm{K}} = 21.8 \pm 0.5$ kcal/mol for the cyclization from *s*-cis **4b** form. More problems arise in the determination of the heat of reaction. The experimental heat of formation, $\Delta H^{\circ}_{\mathrm{f}} = 103 \pm 3$ kcal/mol[15] for α,3-didehydrotoluene **6** does not agree with the values obtained either by bond energy estimates

Scheme 3. Cope vs Bergman Cyclizations and Their Energy Profile



or by means of coupled-cluster computations via isodesmic equations, which give a value of 107.2 ± 2.0 kcal/mol.[16] The ΔH_f° of enyne-allene **4** should be smaller by 1−2 kcal/mol,[5b] so neglecting entropy, $\Delta G_{298\text{ K}}$ should be reduced by 5.5 ± 0.5 kcal/mol. Fortuitously, these errors partially cancel, and the reported comparisons between experimental and computed reaction energies are not terribly off.

The Electronic Structure of *p*-Benzyne and α-3-Didehydrotoluene Biradicals

First, we will see how the different theoretical methods can deal with the electronic structures of biradicals such as *p*-benzyne, **3**, or α-3-didehydrotoluene, **6**. A simple restricted Hartree−Fock (RHF) computation on *p*-benzyne will give an electronic structure with a $|...b_{1u}{}^2a_g{}^0\rangle$ configuration. However, the b_{1u} and a_g orbitals are very close energetically; to construct an appropriate zeroth-order description, one would need a multideterminantal approach that includes excitations from the b_{1u} to the a_g orbitals. Thus, complete active space self-consistent field (CASSCF(2,2)) computations give $\Psi = c_1|...b_{1u}{}^2a_g{}^0\rangle + c_2|...b_{1u}{}^0a_g{}^2\rangle$.[17] For a perfect biradical, the weight of the two configurations will be the same, that is, $|c_1| = |c_2|$, and the singlet−triplet splitting is zero. However, in the case of **3**, one obtains $c_1 \gg c_2$, due to the coupling between the unpaired electrons. Two coupling mechanisms are possible: through-space and through-bond.[18] Whereas the distance between the C^1 and C^4 atoms is too long (>2.6 Å) to make the former significant, through-bond coupling is considerable. Electron pairing leads to an elongation of the C^2-C^3 bond whereas the C^1-C^2 bond is shortened. As we can see in Figure 2, the b_{1u} orbital is especially stabilized over the a_g orbital by the interaction with the σ C−C bonds.

Until now, we are dealing with delocalized orbitals that transform according to the D_{2h} symmetry group of *p*-benzyne. How about our undergraduate vision of a biradical with two electrons in two separate orbitals? These kinds of localized molecular orbitals, ψ_a and ψ_b, can be obtained through a simple combination of delocalized orbitals:

$$\psi_a = \cos\theta\psi_{b_{1u}} + \sin\theta\psi_{a_g} \qquad (1)$$

$$\psi_b = -\sin\theta\psi_{b_{1u}} + \cos\theta\psi_{a_g} \qquad (2)$$

Upon filling these orbitals with electrons of opposite spin, the spatial spin symmetry of the molecule can be maintained and the spin operator expectation value, $\langle S^2\rangle$, will no longer be zero. This is called the unrestricted broken-

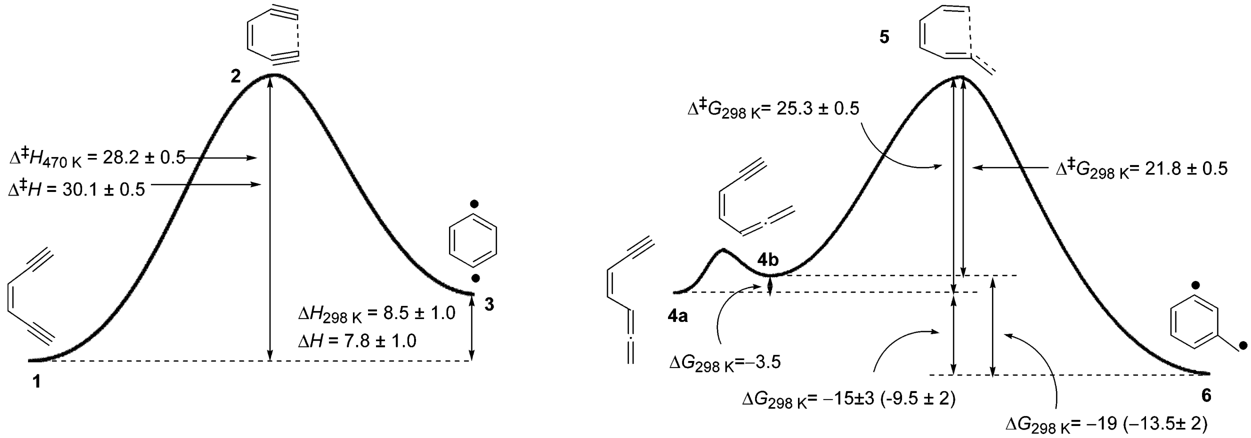


FIGURE 1. Experimental thermochemical data (kcal/mol) for the Bergman and Myers−Saito cyclizations. Best energy estimates for the Myers−Saito reaction are given in parentheses.

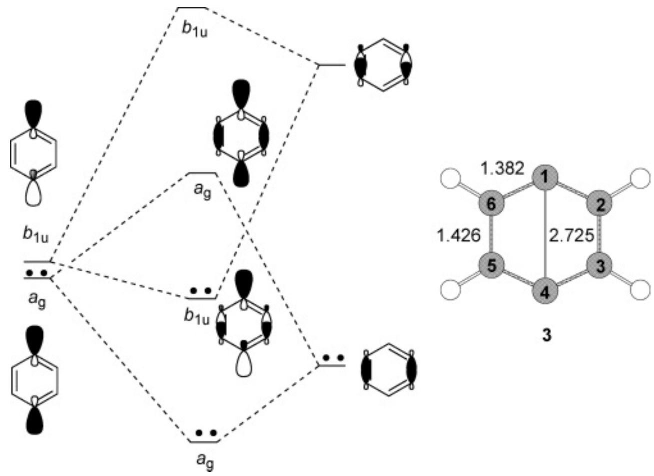


FIGURE 2. MO representation of *p*-benzyne. Bond distances are given in Å at CCSD(T)/6-31G** level.[32]

spin-symmetry solution (UBS). Note that these orbitals do not transform in any of the D_{2h} representations and therefore the full wave function symmetry cannot be utilized in the SCF computation. However, because ψ_a and ψ_b transform through the A_1-C_{2v} representation, it is possible to use symmetry partially. The easiest way to get such broken-spin symmetry solutions is to feed the SCF computation with 50:50 mix (singlet−triplet) initial guess of the HOMO and LUMO orbitals. Although in most cases this approach works acceptably well, we advocate careful examination of the results by visual inspection of the orbitals or by checking the stability of the wave function, because in some cases HOMO and LUMO do not correspond to the orbitals required for proper mixing.[19]

The α-3-didehydrotoluene biradical **6** possesses a $\sigma^1\pi^1$ $^1A''$ ground state with unpaired electrons being localized in orbitals of A′ and A″ symmetry. The RHF description here is even worse than that for the *p*-benzyne case since it will not describe the proper $^1A'$ but rather one of the zwitterionic $^1A'$ states, given by either $\sigma^2\pi^0$ or $\sigma^0\pi^2$ configurations. A single-determinant UBS approach based on HOMO−LUMO mixing for an initial UBS guess is problematic since the orbitals are of different symmetry; the results may be meaningless. In such cases, a much better approach is to compute first an unrestricted triplet wave function for the triplet $^3A''$ state and then simply swap the orbitals to present the proper open-shell singlet state.[20] A similar electronic description is needed for the “Schmittel” product **8**.

Computational Methodology Performance

Multireference and Valence Bond Methods. The first studies on the Bergman reaction used multiconfigurational approaches. Because dynamic correlation is also very important, simple CASSCF results are meaningless (Table 1), because they predominantly include static correlation for a reaction where the bonding pattern changes completely. Either multireference configuration interaction (CI) methods (MRCI)[21] or (expanded) perturbation methods based on CASSCF wave functions such as complete active space with second-order perturbation theory (CASPT2) are necessary. CASPT2[0][22] calculations[23] suffer from the problem that they display systematic failures when the number of paired electrons changes in the reaction, and these methods consequently grossly underestimate the activation barrier as well as the reaction endothermicity for the Bergman reaction. CASPT2[g1][24] and OVBPT2[25] calculations improve the reaction energetics somewhat (Table 1).[26,27] However, multireference Møller−Plesset second-order perturbation theory (MP2) methods, either CASPT2, orthogonal valence bond second-order perturbation (OVBPT2),[27] or the Nakano second-order multiconfigurational quasi-degenerate perturbation (MCQDPT2)[28] method, do not improve significantly the singlet−triplet energy separations as compared to CASSCF results.[29] The MRCI methodology has been also applied by Engels and co-workers in the study of enyne-allene cyclizations.[30] They obtained values for the Myers−Saito and Schmittel C^2-C^6 and C^2-C^7 cyclizations in good agreement with experiment and coupled-cluster computations (Table 2).

In collaboration with the Shaik group, we have also applied a combined density functional theory (DFT)− valence bond (VB) methodology to the study of the Bergman reaction.[31] In this DFT−VB scheme, the inactive orbitals are derived from DFT calculations (BLYP in this case), and then the active VB orbitals are computed in the field of the DFT shell. This methodology overestimates the activation barrier by more than 10 kcal/mol; however, the reaction energy is closer to experiment than in CASSCF calculations (Table 1).

One important aspect is that these methods have much less of blackbox character than single-determinant approaches at the expense of considerable human effort. We will outline below that some single-reference approaches can provide results that are comparable to elaborate multireference calculations.

Coupled-Cluster Methods. Coupled-cluster theory (CC) typically deals well with many multireference problems, especially when the effect of triple excitations is included. However, one of the principal problems in the application of coupled-cluster theory to biradicals is that large-amplitude single excitations potentially lead to instabilities in the cluster expansion. Standard coupled cluster with single, double, and triple excitation (CCSD(T)) calculations give good geometries and energies in the Bergman reaction since single excitations are forbidden by symmetry (vide supra) but for low-symmetry biradicals,[32] single excitations can become important and CCSD(T) provides meaningless results. To alleviate this problem, Brueckner doubles BD(T) calculations were introduced.[33] In this coupled-cluster variant, the orbitals are rotated to eliminate the singles amplitudes in the CCSD expansion. This methodology has proven to be highly successful not only for $\sigma-\sigma$ but also for $\sigma-\pi$ biradicals such as those found in the Myers−Saito and Schmittel cyclizations.[16] In a reasonable computational protocol, a UBS reference with the proper A″ symmetry is first determined by appropriate orbital switching (vide supra). The result is then fed into

Table 1. Computed Activation and Reaction Energies (kcal/mol) for the Bergman Cyclization

Bergman Cyclization

Level	$\Delta^{\ddagger}H$	ΔH		ΔE_{ST} **3**		
Multireference						
CASSCF/TVZ(d,p)[a]				2.7		
CASSCF/ANO[b]	43.6	27.7				
CASPT2[0]/ANO[b]	23.2	2.3				
CASPT2[g1]/ANO[b]	23.9	3.8				
CASPT2/cc-pVDZ[a]				5.8		
MCQDPT2/TVZ(d,p)[a]				5.0		
OVBPT2/6-31G*[c]	34.8	−0.7		0.7		
VB-DFT[d]	46.6	10.1				
Coupled-Cluster						
CCSD(T)/cc-pVDZ[e]	27.7	4.1				
CCSD(T)/cc-pVDZ[e,f]	26.8	4.1		5.3		
BD(T)/cc-pVDZ[e,f]	26.8	4.1		4.9		
BD(T)/cc-pvTZ[e,f,g]	28.9	10.3		3.4		
DFT[h]	RDFT	UBS	UBS_{SF}[i]	UBS	UBS_{SF}[i]	RDFT
SVWN/6-31G**	17.7	−4.6	−7.1	6.1	8.5	4.7
SVWN/cc-pVTZ	19.2	0.6	−1.5	6.6	8.8	5.8
BLYP/6-31G**	25.4	6.8	4.1	4.1	6.9	−1.2
BLYP/cc-pVTZ*	28.6	13.6	10.8	4.5	7.3	0.1
B3LYP/6-31G**	31.2	3.3	1.1	2.5	4.7	−14.8
B3LYP/cc-pVTZ	34.4	10.1	7.8	2.6	4.9	−13.1
B3LYP/6-311+G(3df,3pd)	34.1	10.1	7.8	2.6	4.9	−12.8
Exp. (ΔE)[h]	30.1± 0.5	7.8 ±1.0		3.5±0.5		

[a] Reference 29. [b] C(5s4p2d), H(3s2p), ref 26. [c] Reference 27. [d] Reference 31. [e] Reference 32. [f] On UBS-BPW91/cc-pVDZ geometries. [g] Using extrapolation methods. [h] Reference 13. [i] UBS-DFT sum formulas (eq 3) corrected.

UCCSD(T) or UBD(T) computations (Table 2). Accordingly, when the unrestricted UCCSD(T) method is applied to the Myers–Saito product **6**,[34] the reaction energies are in good agreement with experiment since the strong spin contamination of the reference wave function is annihilated in the CCSD expansion and it does not affect the final results. Another approach consists of mixing the HOMO A′ with the LUMO A″ to get a new pair of delocalized orbitals and then performing a restricted calculation. Here the BD(T) approach is clearly superior since the reference determinant is progressively rotated leading to an optimum mixing,[35] generating a reference determinant with the proper symmetry to describe the biradical. UCCSD(T) or closed shell BD(T) methodologies are also indicated when calculating properties beyond energies and geometries, since RHF based CCSD(T) calculations can suffer from orbital instabilities leading to spurious vibrational frequencies.[36]

Density Functional Methods. The first computational studies on the Bergman reaction led to some confusion since calculations using both restricted[37] and UBS determinants[14,30] were presented in the literature. Restricted calculations led to the conclusion that gradient-corrected generalized gradient approximation (GGA) functionals[38] such as BLYP or BPW91 were superior to hybrid functionals such as B3LYP. However, in an extensive study, Kraka and co-workers[13] analyzed the behavior of several local GGA and hybrid functionals for the desciption of *p*-benzyne and the energetics of the Bergman reaction. They showed that *p*-benzyne[39] is unstable with respect to spatial spin-symmetry breaking and a lower energy solution can be obtained from UBS calculations. The lowering of the energy in going from the restricted to the unrestricted solution grows in the order local-density approximation (LDA) < GGA < hybrid functionals. The inferior performance of pure versus hybrid functionals in the UBS scheme has been attributed to the self-interaction error, which mimics static correlation in DFT theory, being greater in pure than in hybrid functionals.[40] It is therefore a matter of choice whether to use DFT as an empirical method to give qualitatively reasonable results or to try

Table 2. Computed Activation and Reaction Free Energies (kcal/mol) for Myers−Saito and Schmittel Reactions

	C^2−C^7 cyclization[a]		C^2−C^6 cyclization[a]	
	$\Delta^{\ddagger}G_{298\ \mathrm{K}}$	$\Delta G_{298\ \mathrm{K}}$	$\Delta^{\ddagger}G_{298\ \mathrm{K}}$	$\Delta^{\ddagger}G_{298\ \mathrm{K}}$
Multireference				
AM1 (CI = 2)[b]	27	−5	44	20
CAS(10,10)/6-31G*[b]	29 (31)	4 (8)	37	18
MR-CI+Q/6-31G*[b]	25 (27)	−21 (−17)	35	12
Coupled-Cluster				
CCSD(T)/6-31G**[c,d]	22.0	−60.6[e]		
BD(T)/6-31G**[c,d]	22.0	−11.2[e]		
UCCSD(T)/6-31G**[c,f]	22.3	−12.4		
UBD(T)/6-31G**[c,f]	22.2	−14.1		
CCSD(T)/cc-pVDZ[g]	22.2	−24.3	35.0	17.3
BD(T)/cc-pVDZ[g]	22.2	−11.9	34.8	10.0
DFT				
UBS-BLYP/6-31G*[g]	20.2	−7.8	31.5	14.2
UBS-BLYP/cc-pVTZ[g]	22.7	−2.1	34.4	19.3
UBS-B3LYP/6-31G*[h]	24.0	−13.6	31.4	10.9
REKS-BLYP/6-31G*[i]	20.0	−8.3	33.4	16.5
expt[j]	21.8 ± 0.5	−13.5 ± 2	*k*	*k*

[a] From the **4b** *s*-cis conformer. [b] Reference 30a. ΔH values are provided; in parentheses $\Delta G_{298\ \mathrm{K}}$ values calculated with help of DFT thermal corrections from ref 34 are given. [c] ΔH, single-point energy on UB3LYP/6-311G** geometries. [d] Results unpublished. Frozen core computations. [e] Mixing HOMO−LUMO (guess=mix). [f] Reference 34. Full space calculations. [g] Reference 16. Single-point energy on UBS-BLYP/6-31G* geometries. [h] Unpublished. [i] ΔH_0 values, ref 44c. [j] Reference 5c, see text. [k] Not applicable.

to improve a reformulated DFT as an ab initio method that also attempts quantitative accuracy.

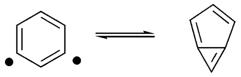
It was also suggested that B3LYP results can be improved by using a sum formula where the energy of the pure singlet state (E(S), eq 3) can be estimated under the assumption that spin contamination is mainly introduced through the first triplet state.[13] The amount x of spin contamination is determined from the spin-squared expectation values $\langle S^2\rangle$ obtained directly from the Slater determinants, through eq 4. Calculations on a larger number of systems are needed to check whether this approach is generally applicable.

$$E(\mathrm{S}) = \frac{1}{x}\,E(\mathrm{UDFT,S}) - \frac{1-x}{x}E(\mathrm{T}) \qquad (3)$$

$$x = \frac{\langle S^2\rangle_{\mathrm{UDFT,2S}} - \langle S^2\rangle_{\mathrm{2T}}}{\langle S^2\rangle_{\mathrm{2S}} - \langle S^2\rangle_{\mathrm{2T}}} \qquad (4)$$

However, even for the unrestricted formalism there are pathological cases such as *m*-benzyne **12** where the use of a hybrid functional can lead to misleading results. Thus, Hess[41] proposed a bicyclic anti-Bredt olefin **13** as the observed species in matrix isolation experiments based on B3LYP-calculated energies and comparison of computed vibrational frequencies against experiment (Scheme 4). Further studies showed the BLYP description of the potential surface to be much closer to benchmark CCSD(T) and MRCI calculations.[42] Also the BLYP-computed IR spectrum of **12** is in much better agreement with experiment than that obtained with B3LYP.[43] The poor performance of the B3LYP functional is due to the very large ΔE_{ST} for *m*-benzyne by means of introducing the high-energy first triplet state into the DFT wave function. The BLYP computation does not suffer from this problem because the Kohn−Sham determinant remains stable in a much larger segment of the examined potential energy surface.

Scheme 4. *m*-Benzyne Isomerism



12 **13**

A new promising option to treat multireference problems in DFT is the spin-restricted ensemble-referenced Kohn−Sham method (REKS).[18,44] The idea of this method is that for a system with two quasi-degenerate Kohn−Sham orbitals, ϕ_{r} and ϕ_{s}, the electronic density can be expressed as a function of fractional occupation numbers, n_{r} and n_{s}. These are determined by self-consistent calculations with the one-particle orbitals. REKS BLYP/6-31G* computations give activation and reaction energies for Myers−Saito and Schmittel cyclizations[44c] in good agreement with our "benchmark" BD(T)/cc-pVDZ calculations. Excellent results were obtained with this method for the determination of singlet−triplet splittings of benzynes.[44b]

Recently, we have tested the performance of several combinations of functionals and basis sets in the description of the Bergman and Myers−Saito reactions.[45] This study showed that extension from a medium-sized basis set such as 6-31G* to larger basis set such as 6-311G** or cc-pVTZ does not necessarily improve the behavior of pure functionals. In this respect, B3LYP behaves more predictably. One possible explanation may be that the Bergman and Myers−Saito reactions can suffer from a strong intramolecular basis set superposition error (BSSE) due to the compact structure of the transition states and reaction products. It appears that for the BLYP functional the use of a medium-sized basis such as 6-31G* partially hides the overestimation of the endothermicity of the Bergman reaction. The basis set size has a rather small effect on the geometries; large basis set (triple-ζ quality) single-point energy calculations on double-ζ quality optimized geometries give as good thermochemical values as optimization with the larger basis set.[46] Properties such as ΔE_{ST},[13] which are expected not to be influenced by BSSE, are much less dependent on the basis set size.

In conclusion, the use of the UBS DFT methodology can give quite good results for the cyclizations of polyunsaturated systems. Whereas optimizations with medium-sized basis sets (e.g., 6-31G*) are acceptable, the energies must be computed with larger basis sets (triple-ζ or better). The use of single-point coupled-cluster computations on the DFT geometries provides even better (and more reliable) results with the caveat that closed-shell BD(T) may be required for low-symmetry biradicals.

Applications

Aromaticity and Substituent Effects. Examination of the magnetic properties of the Bergman reaction using the nucleus-independent chemical shifts (NICS) methodol-

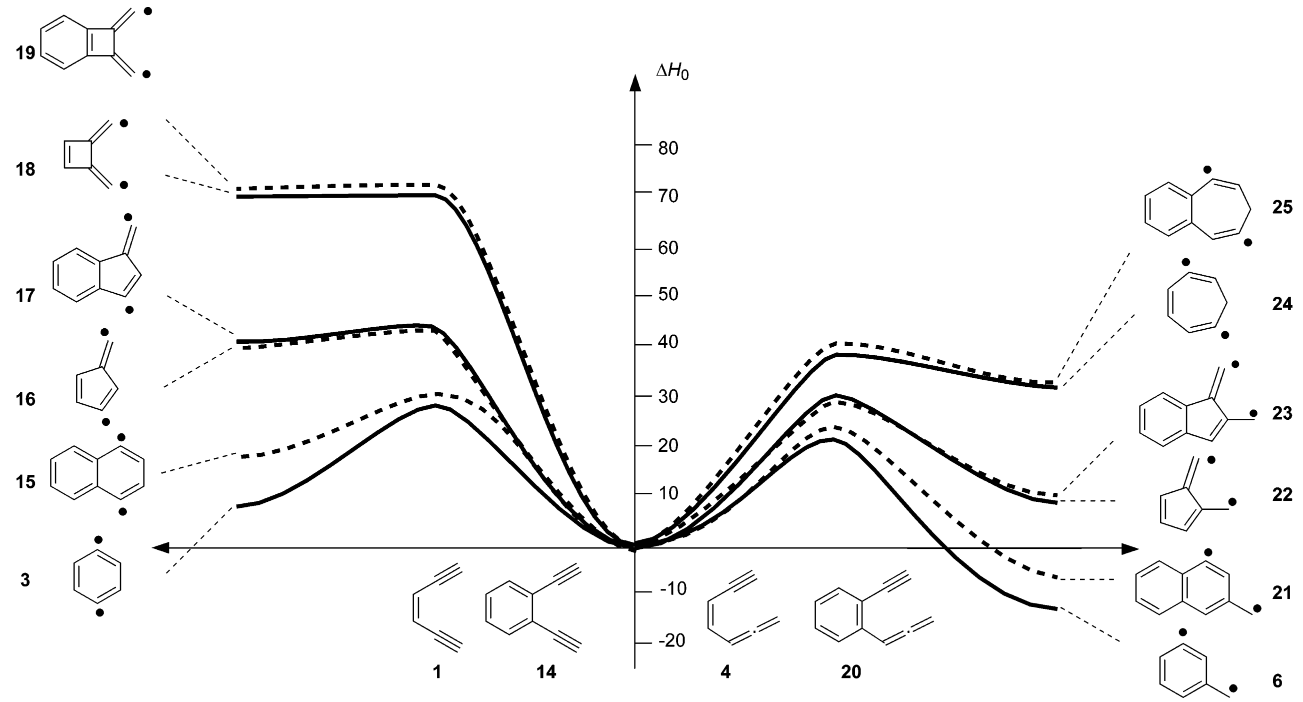


FIGURE 3. BD(T)/cc-pVDZ//UBS-BLYP/6-31G* energy profiles for thermal cyclizations of enediynes and enyne-allenes.

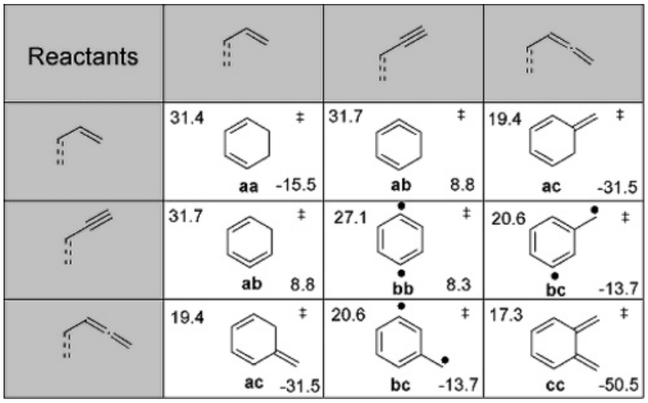


FIGURE 4. Part of the Cope reaction family including the title transformations. In left-top and right-bottom corners of the cells, we give activation and reaction enthalpies (ΔH_0) at the BD(T)/cc-pVDZ// UBLYP/6-31G* level from ref 8.

ogy[47] shows that both the transition structure **2** and the biradical product **3** have large negative NICS values (these are generally taken as indicators of aromaticity). While the analysis of the NICS results with the help of resonance energies taken from VB[31] leads to the conclusion that σ-aromaticity plays a more important role than π-aromaticity, later computations[48] using dissected NICS, that is, isolating contributions from orbitals of different symmetry, showed that the orbitals of π symmetry contribute also significantly to the total NICS.[49] Additional studies should clarify this issue. Transition states for Myers–Saito and Schmittel cyclizations showed moderately negative NICS values.

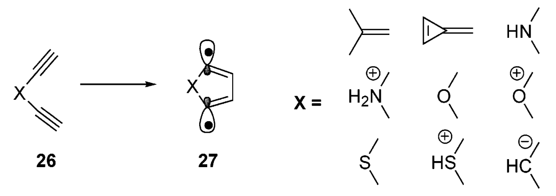
The analysis of the aromaticity and the frontier orbitals revealed that substitution by strong π-electron donors and σ-acceptors (such as $-F$, $-OH$, $-NH_3^+$, $-OH_2^+$) at the alkyne termini of enediynes strongly favors the Bergman cyclization both kinetically, due to increased π-aromaticity and reduced in-plane electron density in the transition state, and also thermodynamically owing to the ability of these groups to stabilize alkenes better than alkynes. π-Electron-withdrawing groups (e.g., $-BH_2$, $-AlH_2$) have the opposite effect and raise the barriers as well as the endothermicities for cyclizations.[49,50]

Overall, aromaticity plays an unexpectedly minor role in these cyclization reactions. This is particularly true for heteroatom enyne-allenes where antiaromatic structures can energetically be *en par* with aromatic ones (see Schemes 5 and 6).

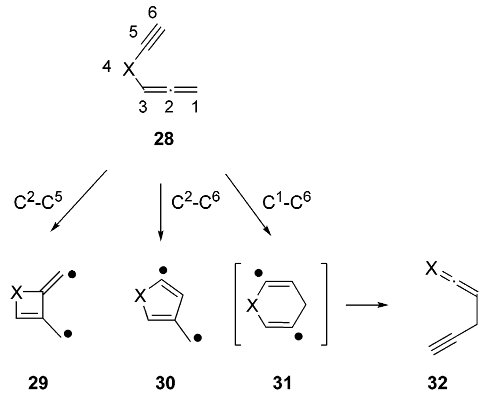
In Search for New Reactions. Hydrocarbons. In the last years our research group has systematically computed new reaction modes of polyunsaturated hydrocarbon systems. We evaluated alternatives to the experimentally known cyclization modes of enediyne **1** and enyne-allene **4**.[45] While the C^2-C^4 cyclizations leading to cyclobutenyl biradicals **18** and **19** are accompanied by very high reaction energies and enthalpies (Figure 3), the C^1-C^5 reaction, leading to fulvene biradicals **16** and **17**, seems more experimentally feasible. For enyne-allenes **4** and **20**, we have found a new C^1-C^7 cyclization mode, leading to the $\sigma-\sigma$ cycloheptatriene biradicals **24** and **25**, which is associated with a barrier of 37.4 kcal/mol, 10 kcal/mol above that of the Schmittel cyclization. Note the effect of benzannulation on decreasing the difference between the activation barriers of the Myers–Saito and Schmittel reactions and enthalpically disfavoring the formation of the aromatic products **15** and **21**.

We have also recently shown that Bergman and related reactions of polyunsaturated hydrocarbons[8] with a 1,3,5-hexatriene skeleton form a branch (Figure 4) inside a larger "Cope" reaction family characterized by a common 1,5-hexadiene structural unit. Examination of this whole family allowed us to derive a very simple rule for involve-

Scheme 5. Bergman-type Reaction of 1,4-Pentadiynes to "Aromatic" 27



Scheme 6. Cyclization of 4-Heteroatom-1,2-hexadiene-5-ynes 28



ment of transient biradicals in Cope-like reactions of hydrocarbons: *a nonconcerted reaction takes place when biradical intermediates are stabilized either by allyl or aromatic resonance.*

Heterosubstitued Systems. The Bergman-type cyclization of hetero 1,5-pentadiynes **26** is in nearly all cases a highly disfavored reaction with barriers above 50 kcal/mol at UBS−BLYP/6-311+G* (Scheme 5). Only in the case that $X = OH^+$, that is, a σ-acceptor and a π-donor ($\Delta^{\ddagger}H = 34.4$, $\Delta H = -4.7$ kcal/mol) the reaction may be experimentally feasible.[51] This is particularly striking because the aromaticity in the protonated product ($X = OH^+$) is much reduced. Hence, electronic effects transmitted through the σ-framework are clearly dominant (vide supra).

We have also examined several cyclization modes of 4-heteroatom-1,2-hexadiene-5-yne systems **28** (Scheme 6),[52] where the central double bond of enyne-allene **4** is substituted by a heteroatom X. The C^2−C^5 Schmittel-like cyclization mode is quite disfavored kinetically with barriers in the range of 35−50 kcal/mol, whereas the C^2−C^6 mode, analogous to the Myers−Saito reaction, is much more favorable especially when X is a strong π-electron donor or σ-donor. However, the barriers for the C^1−C^6 cyclization are generally lower than those for the C^2−C^6 mode. In most cases, the transition state does not lead to biradical **31** but to enyne-heteroallene **32**, resulting in a Claisen-type rearrangement.

Concluding Remarks

The use of DFT in an unrestricted broken-symmetry approach has proven to be a practical tool for the study of enediyne and enyne-allene cyclizations. Much more elaborate multireference calculations are desirable but not needed for qualitative purposes. Modern empirical GGA functionals furnish good results that can be further improved by the use of single-point coupled-cluster energy computations on DFT geometries.

On the basis of this time-saving computational approach, our group has shown that the intermediacy of biradicals in Cope-type rearrangements, to which the Bergman and Myers−Saito reactions belong, can be predicted using a very simple rule: biradicals are likely to be intermediates if they are stabilized either by allyl resonance or by aromaticity.

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