Myers−Saito versus C^2-C^6 ("Schmittel") Cyclizations of Parent and Monocyclic Enyne−Allenes: Challenges to Chemistry and Computation

Peter R. Schreiner* and Matthias Prall

Contribution from the Institute of Organic Chemistry, Georg-August-Universität Göttingen, Tammannstrasse 2, D-37077 Göttingen, Germany

Received April 21, 1999. Revised Manuscript Received June 22, 1999

Abstract: The Myers−Saito and the C^2-C^6 cyclization ("Schmittel" cyclization) of the parent enyne−allene (*Z*)-1,2,4-heptatriene-6-yne were investigated with pure density functional theory (DFT) methods and were compared to coupled cluster [CCSD(T)] and Brueckner doubles [BCCD(T)] high-level calculations. Both the Becke−Lee−Yang−Parr (BLYP) and the Becke−Perdew−Wang (BPW91) DFT levels with the 6-31G(d) basis sets are quite suitable to describe the cyclization barriers and are nearly as accurate as much more time-consuming high-level methods. As noted before for the Bergman-cyclization, the hybrid functional B3LYP yields good geometries but is less suitable for energies due to Hartree−Fock mixing. Single-point energy evaluations with the much larger cc-pVTZ basis set do not necessarily improve the results; some even become worse. The computed enthalpy of formation ($\Delta H_f°$) of the Myers−Saito product (107 ± 4 kcal mol^{-1}) compares relatively well to the experimental value (103 ± 3 kcal mol^{-1}) where an upward correction within the error bars seems indicated. Using isodesmic equations, the $\Delta H_f°$ of the Schmittel product is predicted to be 129 ± 4 kcal mol^{-1}. Since BLYP describes the barriers of the parent enyne−allene system quite well, it was utilized to compute the cyclizations of monocyclic enyne−allenes (ring sizes = 7−10 carbons). The Myers−Saito cyclization of the nine-membered ring is associated with the smallest reaction barrier and the highest exothermicity. While ring strain effects are not able to favor the Schmittel products much over the Myers−Saito products, the eight-membered ring closures should give rise to a mixture of both products. The singlet−triplet separations of all cyclization products are very small (1 kcal mol^{-1}); the hydrogen-abstracting ability of such cyclic systems should therefore be rather high.

Introduction

The cyclization reactions of the enediyne and enyne−allene moieties of the natural antitumor antibiotics neocarzinostatin (**1**), calicheamicin (**4**), and dynemicin (**5**), as well as others, lead to highly reactive biradicals which are held responsible for the DNA cleavage abilities of these potent pharmacophors. Neocarzinostatin was first isolated from *Streptomyces carzinostaticus* in 1961[1] and consists of the active chromophore **1** (Scheme 1) bound to a 113 amino acid apoprotein.[2,3] The enediyne carbocycle of **1** is activated by a thiol and rearranges to enyne−cumulene **2**, which cyclizes to the highly reactive biradical **3** (Scheme 1).[4] As **1** binds to the minor groove of DNA,[5−7] **3** is able to abstract hydrogens from adenine or thymine moieties leading to cell destruction.[2] While calicheamicin **4** and dynemicin **5** (Scheme 1) undergo Bergman cyclizations to give rise to 1,4-didehydrobenzene biradicals, the neocarzinostatin chromophore **1** shows a different reaction pattern.

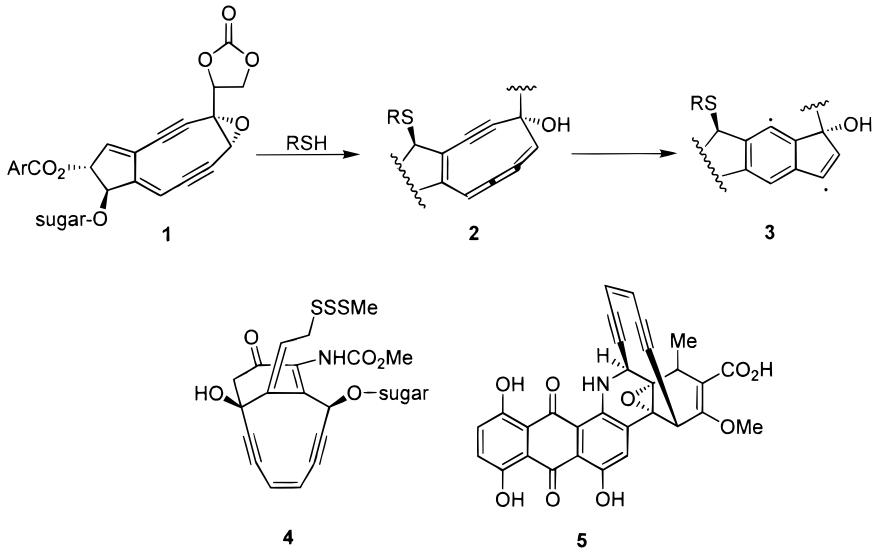
In a beautiful series of experiments, Myers and independently Saito *et al*. demonstrated that enyne−allenes **7** show similar reactivity patterns as the enyne−cumulene core **6** (Scheme 2).[8−11] The C^2-C^7 cyclization, now known as the "Myers−Saito cyclization", of **7** gives rise to α,3-didehydrotoluene (**8**) and toluene derivatives (**9**) after abstraction of hydrogens from suitable donors such as DNA. In contrast to the endothermic (8.5 ± 1.0 kcal mol^{-1})[12] Bergman cyclization, the Myers−Saito reaction is considerably exothermic (-15 ± 3 kcal mol^{-1} or less, *vide infra*).[9] In addition, the cyclization products **8** are partially conjugated σ,π-biradicals[9] which are less reactive than the σ,σ-biradicals obtained from Bergman-type cyclizations.[11,13] Nicolaou *et al*. showed that phosphine oxide substituted enyne−allenes are relatively stable and cyclize smoothly at physiological temperatures to give DNA-cleaving biradicals.[13] This clearly demonstrates that enyne−allene derivatives are potent cytotoxics against cancer cells.

* Corresponding author. E-mail: pschrei@gwdg.de.

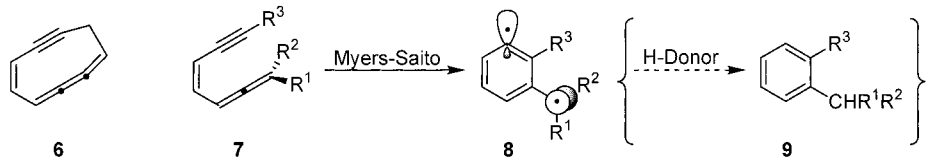
(1) Ishida, N.; Miyazaki, K.; Kumagai, K. M.; Rikimaru, M. *J. Antibiot.* **1965**, *18*, 68−76.
(2) Nicolaou, K. C.; Dai, W.-M. *Angew. Chem.* **1991**, *103*, 1453−1481.
(3) Wisniewski-Grissom, J.; Gunawardena, G. U.; Klingberg, D.; Huang, D. H. *Tetrahedron* **1996**, *52*, 6453−6518.
(4) Brückner, R.; Suffert, J.; Abraham, E.; Raeppel, S. *Liebigs Ann.* **1996**, 447−456.
(5) Lee, S. H.; Goldberg, I. H. *Biochemistry* **1989**, *28*, 1019−1026.
(6) Goldberg, I. H. *Free Radicals Biol. Med.* **1987**, *3*, 41.
(7) Povirk, L. F.; Dattagupta, N.; Warf, B. C.; Goldberg, I. H. *Biochemistry* **1981**, *20*, 4007−4014.
(8) Myers, A. G.; Kuo, E. Y.; Finney, N. S. *J. Am. Chem. Soc.* **1989**, *111*, 8057−8059.
(9) Myers, A. G.; Dragovich, P. S.; Kuo, E. Y. *J. Am. Chem. Soc.* **1992**, *114*, 9369−9386.
(10) Saito, K.; Watanabe, T.; Takahashi, K. *Chem. Lett.* **1989**, 2099−2102.
(11) Saito, I.; Nagata, R.; Yamanaka, H.; Murahashi, E. *Tetrahedron Lett.* **1990**, *31* (20), 2907−2910.
(12) Roth, W. R.; Hopf, H.; Horn, C. *Chem. Ber.* **1994**, *127*, 1765−1779.
(13) Nicolaou, K. C.; Maligres, P.; Shin, J.; de Leon, E.; Rideout, D. *J. Am. Chem. Soc.* **1990**, *112*, 7825−7826.

10.1021/ja991282+ CCC: $18.00
Published on Web 09/03/1999

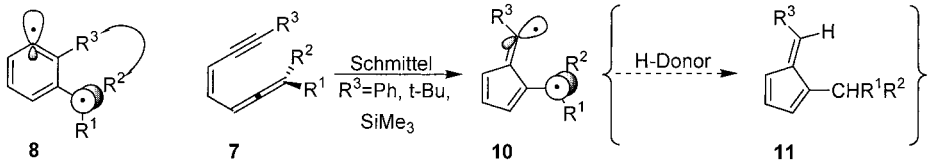
Scheme 1. Cyclization Reactions of the Neocarzinostatin Chromophore **1** and the Bergman-Type Enediyne Antibiotics Calicheamicin **4** as well as Dynemicin A **5**



Scheme 2. Enyne-Cumulene Core **6** and the Myers−Saito Cyclization Reaction of Enyne−Allenes **7**



Scheme 3. New C^2-C^6 Cyclization ("Schmittel" Cyclization) of Substituted Enyne−Allenes **7**



Although the conjugated π-system of enyne−allenes **7** may offer a wide variety of cyclization modes, only the Myers−Saito products **8** were obtained until Schmittel *et al*. demonstrated that **7** also may undergo a novel C^2-C^6 ring closure leading to methyl fulvene derivatives **10** (Scheme 3).[14−18] For convenience, we will henceforth refer to the C^2-C^6 cyclization as the "Schmittel" cyclization. Although the Myers−Saito reaction is generally energetically much more favorable, Schmittel *et al*. were able to show that the methyl fulvenes **10** can be obtained as the main products when the alkyne terminal hydrogen is replaced by phenyl[18] or bulky groups such as *tert*-butyl or trimethylsilyl.[19,20] These substituents raise the cyclization barrier of the Myers−Saito reaction due to steric hindrance in **8** (Scheme 3) and, in the case of phenyl, lower the barrier of the Schmittel cyclization by radical stabilization through conjugation.[15] Experimental analyses suggest that the Schmittel products **10** also are σ,π-biradicals just as the Myers−Saito intermediates. The DNA-cleaving ability of **10** strongly support their biradical nature.[15,16]

Background

The Myers−Saito[8,21] and Schmittel[18,22,23] reactions received much less attention[24−27] than the Bergman cyclization,[28−30] which was extensively studied computationally.[31−46] These

(14) Schmittel, M.; Strittmatter, M.; Kiau, S. *Angew. Chem.* **1996**, *108* (16), 1952−1954.
(15) Schmittel, M.; Kiau, S.; Siebert, T.; Strittmatter, M. *Tetrahedron Lett.* **1996**, *37* (43), 7691−7694.
(16) Schmittel, M.; Steffen, J.-P.; Auer, D.; Maywald, M. *Tetrahedron Lett.* **1997**, *38* (35), 6177−6180.
(17) Schmittel, M.; Keller, M.; Kiau, S.; Strittmatter, M. *Chem. Eur. J.* **1997**, *3* (5), 807−816.
(18) Schmittel, M.; Strittmatter, M.; Kiau, S. *Tetrahedron Lett.* **1995**, *36* (28), 4975−4978.
(19) Gillmann, T.; Hülsen, T.; Massa, W.; Wocadlo, S. *Synlett* **1995**, 1257−1259.
(20) Rodriguez, A.; Garcia, J. G.; Ramos, B.; Pratt, L. M. *Tetrahedron Lett.* **1995**, *36(41)*, 7391−7394.
(21) Nagata, R.; Yamanaka, H.; Okazaki, E.; Saito, I. *Tetrahedron Lett.* **1989**, *30*, 4995−4998.
(22) Schmittel, M.; Strittmatter, M.; Kiau, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1843−1845.
(23) Schmittel, M.; Strittmatter, M.; Vollmann, K.; Kiau, S. *Tetrahedron Lett.* **1996**, *37* (7), 999−1002.
(24) Sander, W.; Wandel, H.; Bucher, G.; Gräfenstein, J.; Kraka, E.; Cremer, D. *J. Am. Chem. Soc.* **1998**, *120*, 8480−8485.
(25) Koga, N.; Morokuma, K. *J. Am. Chem. Soc.* **1991**, *113*, 1907−1911.
(26) Engels, B.; Lennartz, C.; Hanrath, M.; Schmittel, M.; Strittmatter, M. *Angew. Chem.* **1998**, *110*, 2067−2070.
(27) Engels, B.; Hanrath, M. *J. Am. Chem. Soc.* **1998**, *120*, 6356−6361.
(28) Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25−31.
(29) Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660−661.
(30) Hoffmann, R. W. *Dehydrobenzene and Cycloalkynes*; Academic Press: New York, 1967.
(31) Lindh, R.; Persson, B. J. *J. Am. Chem. Soc.* **1994**, *116*, 4963−4969.
(32) Lindh, R.; Schütz, M. *Chem. Phys. Lett.* **1996**, *258*, 409−415.
(33) Lindh, R.; Lee, T. J.; Bernhardsson, A.; Persson, B. J.; Karlström, G. *J. Am. Chem. Soc.* **1995**, *117*, 7186−7194.
(34) Kraka, E.; Cremer, D.; Bucher, G.; Wandel, H.; Sander, W. *Chem. Phys. Lett.* **1997**, *268*, 313−320.

reactions are technically quite challenging as closed-shell structures develop an open-shell character to a large degree during the cyclization, leading to significant configurational mixing. The pronounced antitumor reactivity[47] and physical measurements[48] show that all cyclization products have small singlet−triplet energy separations (ΔE_{ST}), *i.e.*, they have high degrees of biradical character.[48,49] As a consequence, single-determinant (*e.g.*, Hartree−Fock, SCF) approaches are generally inadequate for such systems. Multireference techniques such as the complete active space SCF (CASSCF) method account for nondynamic electron correlation; chemically accurate results are only obtained if dynamic correlation is also considered at, for instance, CASPT2 (a variant of CASSCF which includes Møller−Plesset perturbation theory)[50−52] or multireference configuration interaction (MRCI) levels of theory in conjunction with large basis sets. These two approaches, however, suffer from systematic errors when the number of unpaired electrons changes along the reaction coordinate (for CASPT2),[53] as is the case for all of the above cyclizations, or when the structures under consideration become relatively large (size-consistency problem of the CI Ansatz;[54] in part remedied by the Davidson correction,[55,56] denoted as +Q). Furthermore, CASPT2 and MRCI approaches are computationally very demanding despite new and promising algorithms.[57] Equally taxing are variants of coupled-cluster theory[58−63] which utilize excitations from a Hartree−Fock reference wave function accounting for a major fraction of the total correlation energy. Hence, this approach often works well, especially if triple excitations are included perturbatively {CCSD(T)},[59,63] in many instances even for multireference cases. However, low-symmetry biradicals having narrow ΔE_{ST}'s may lead to instabilities for the CCSD(T) solution, requiring the use of, *e.g.*, Brueckner-type orbitals[64−68] which eliminate the contributions from single-excitations {*i.e.*, BCCD(T), or short Brueckner doubles, BD}.[45,69] All of these elaborate schemes are time-consuming and very often become prohibitive when structures of interest to experimentalists are under consideration.

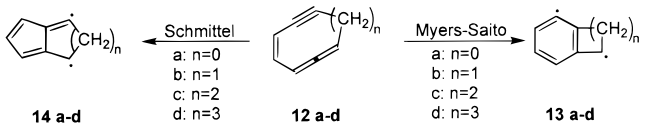
An alternative is offered by density functional theory (DFT) approaches,[70−74] where the electron density and not the wave function is the basic variable which determines all properties of a molecular system. As a consequence, the concept of orbital occupations (the physics of HF and DFT orbitals is different) and configurations is not as clear cut as in traditional, HF-based theory. Furthermore, multireference-type structures which give similar densities for the configurations in question may be treated exceptionally well with DFT. A case in point is DFT applications to carbenes,[75−87] which used to be *the* classical domain for CI theory.[88] The situation is more complex when

(35) Kraka, E.; Cremer, D. *J. Am. Chem. Soc.* **1994**, *116*, 4929−4936.
(36) Schreiner, P. R. *J. Chem. Soc., Chem. Commun.* **1998**, 483−484.
(37) Schreiner, P. R. *J. Am. Chem. Soc.* **1998**, *120*, 4184−4190.
(38) Scheiner, A. C.; Schaefer, H. F., III; Liu, B. *J. Am. Chem. Soc.* **1989**, *111*, 3118−3124.
(39) Nicolaides, A.; Borden, W. T. *J. Am. Chem. Soc.* **1993**, *115*, 11951−11957.
(40) Cramer, C. J.; Nash, J. J.; Squires, R. R. *Chem. Phys. Lett.* **1997**, *277*, 311−320.
(41) Wierschke, S. G.; Nash, J. J.; Squires, R. R. *J. Am. Chem. Soc.* **1993**, *115*, 11958−11967.
(42) Hoffner, J.; Schottelius, M. J.; Feichtinger, D.; Chen, P. *J. Am. Chem. Soc.* **1998**, *120*, 376−385.
(43) Logan, C. F.; Chen, P. *J. Am. Chem. Soc.* **1996**, *118*, 2113−2114.
(44) Chen, W.-H.; Chang, N.-Y.; Yu, C.-H. *J. Phys. Chem.* **1998**, *102*, 2584−2593.
(45) Cramer, C. J. *J. Am. Chem. Soc.* **1998**, *120*, 6261−6269.
(46) Cramer, C. J.; Squires, R. R. *J. Phys. Chem. A* **1997**, *101*, 9191−9194.
(47) Chen, P. *Angew. Chem.* **1996**, *108*, 1584−1585.
(48) Wenthold, P. G.; Squires, R. R.; Lineberger, W. C. *J. Am. Chem. Soc.* **1998**, *120*, 5279−5290.
(49) Wenthold, P. G.; Wierschke, S. G.; Nash, J. J.; Squires, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 7378−7392.
(50) Andersson, K.; Malmqvist, P.-Å.; Roos, B. O.; Sadlej, A. J.; Wolinski, K. *J. Phys. Chem.* **1990**, *94*, 5483−5488.
(51) Andersson, K.; Malmqvist, P.-Å.; Roos, B. O. *J. Phys. Chem.* **1992**, *96*, 1218.
(52) Andersson, K.; Roos, B. O. Multiconfigurational Second-Order Perturbation Theory. In *Modern Electronic Structure Theory I*; Yarkony, D. R., Ed.; World Scientific: Singapore, 1995; pp 55−109.
(53) Andersson, K.; Roos, B. O. *Int. J. Quantum. Chem.* **1993**, *45*, 591−607.
(54) Cársky, P. Configuration Interaction. In *The Encyclopedia of Computational Chemistry*; Schleyer, P. v. R., Allinger, N. L., Clark, T., Gasteiger, J., Kollman, P. A., Schaefer, H. F., III, Schreiner, P. R., Eds.; John Wiley & Sons: Chichester, 1998; pp 485−497.
(55) Del Bene, J. B.; Stahlberg, E. A.; Shavitt, I. *Int. J. Quantum Chem. Quantum Chem. Symp.* **1990**, *24*, 455−466.
(56) Langhoff, S. R.; Davidson, E. R. *Int. J. Quantum. Chem.* **1974**, *8*, 61−72.
(57) Engels, B.; Hanrath, M. *Chem. Phys.* **1997**, *225*, 197−202.
(58) Gauss, J. Coupled-Cluster Theory. In *The Encyclopedia of Computational Chemistry*; Schleyer, P. v. R., Allinger, N. L., Clark, T., Gasteiger, J., Kollman, P. A., Schaefer, H. F., III, Schreiner, P. R., Eds.; John Wiley & Sons: Chichester, 1998.
(59) Scuseria, G. E. *Chem. Phys. Lett.* **1991**, *176*, 27−35.
(60) Scheiner, A. C.; Scuseria, G. E.; Lee, T. J.; Rice, J. E.; Schaefer, H. F., III *J. Chem. Phys.* **1987**, *87*, 5391.
(61) Purvis, G. D., III; Bartlett, R. J. *J. Chem. Phys.* **1982**, *76*, 1910−1918.
(62) Urban, M.; Noga, J.; Cole, S. J.; Bartlett, R. J. *J. Chem. Phys.* **1985**, *83*, 4041−4046.
(63) Bartlett, R. J.; Watts, J. D.; Kucharski, S. A.; Noga, J. *Chem. Phys. Lett.* **1990**, *165*, 513−522.
(64) Brueckner, K. A. *Phys. Rev.* **1954**, *96*, 508.
(65) Scuseria, G. E. *Chem. Phys. Lett.* **1994**, *226*, 251−256.
(66) Kobayashi, R.; Koch, H.; Jørgensen, P.; Lee, T. J. *Chem. Phys. Lett.* **1993**, *211*, 94−100.
(67) Scuseria, G. E.; Schaefer, H. F., III *Chem. Phys. Lett.* **1987**, *142*, 354−358.
(68) Nesbet, R. K. *Phys. Rev.* **1958**, *109*, 1632.
(69) Handy, N. C.; Pople, J. A.; Head-Gordon, M.; Raghavachari, K.; Trucks, G. W. *Chem. Phys. Lett.* **1989**, *164*, 185−192.
(70) Labanowski, J. K.; Andzelm, J. W. *Density Functional Methods in Chemistry*; Springer-Verlag: Berlin, 1991.
(71) Seminario, J. M.; Politzer, P. *Modern Density Functional Theory: A Tool for Chemistry*; Elsevier: Amsterdam, 1995.
(72) Parr, R. G.; Yang, W. *Density Functional Theory of Atoms and Molecules*; Oxford University Press: New York, 1989.
(73) Gill, P. M. W. Density Functional Theory (DFT), Hartree−Fock (HF), and the Self-Consistent Field. In *The Encyclopedia of Computational Chemistry*; Schleyer, P. v. R., Allinger, N. L., Clark, T., Gasteiger, J., Kollman, P. A., Schaefer, H. F., III, Schreiner, P. R., Ed.; John Wiley & Sons: Chichester, 1998; pp 678−689.
(74) Hu, C.-H.; Chong, D. P. Density Functional Applications. In *The Encyclopedia of Computational Chemistry*; Schleyer, P. v. R., Allinger, N. L., Clark, T., Gasteiger, J., Kollman, P. A., Schaefer, H. F., III, Schreiner, P. R., Ed.; John Wiley & Sons: Chichester, 1998; pp 664−678.
(75) Bettinger, H. F.; Schreiner, P. R.; Schleyer, P. v. R.; Schaefer, H. F., III *J. Phys. Chem.* **1996**, *100*, 16147−16154.
(76) Bettinger, H. F.; Schleyer, P. v. R.; Schreiner, P. R.; Schaefer, H. F., III Computational Analyses of Prototype Carbene Structures and Reactions. In *Modern Electronic Structure Theory and Applications to Organic Chemistry*; Davidson, E. L., Ed.; World Scientific: London, 1997; pp 89−171.
(77) Bettinger, H. F.; Schreiner, P. R.; Schleyer, P. v. R.; Schaefer, H. F., III *J. Org. Chem.* **1997**, *62*, 9267−9275.
(78) Bettinger, H. F.; Schreiner, P. R.; Schleyer, P. v. R.; Schaefer, H. F., III In *Carbenes − A Testing Ground for Electronic Structure Methods; in The Encyclopedia of Computational Chemistry*; Schleyer, P. v. R., Allinger, N. L., Clark, T., Gasteiger, J., Kollman, P. A., Schaefer, H. F., Schreiner, P. R., Eds.; John Wiley & Sons: Chichester, 1998; pp 183−196.
(79) Worthington, S. E.; Cramer, C. J. *J. Phys. Org. Chem.* **1997**, *10*, 755−767.
(80) Cramer, C. J.; Dulles, F. J.; Falvey, D. E. *J. Am. Chem. Soc.* **1994**, *116*, 9787−9788.
(81) Matzinger, S.; Fülscher, M. P. *J. Phys. Chem.* **1995**, *99*, 10747−10751.
(82) Matzinger, S.; Bally, T.; Patterson, E. V.; McMahon, R. J. *J. Am. Chem. Soc.* **1996**, *118*, 1535−1542.
(83) Sulzbach, H. M.; Bolton, E.; Lenoir, D.; Schleyer, P. v. R.; Schaefer, H. F. *J. Am. Chem. Soc.* **1996**, *118*, 9908−9914.

different functionals are considered. For instance, although the gradient-corrected B3LYP (Becke3−Lee−Yang−Parr) functional[89−91] is generally assumed to be the best for structures and energies,[92,93] it is much less well-behaved when it comes to biradicals such as *para*-benzyne and related species, where B3LYP is clearly inferior to *pure* density functional approaches such as BLYP,[36,37] BPW91,[40,45,46] and others.[44,94] Although DFT recovers a significant amount of the electron dynamic correlation energy, it is less successful in treating static correlation between electrons in the same region of space. In addition, unrestricted DFT computations sometimes do not account properly for spatial and spin symmetries for open-shell systems. Fortunately, the critical biradicals in the present study are rather remote and, due to their σ,π-character "disjoint", *i.e.*, they do not occupy the same space at the same time.[95−97]

Schmittel *et al.* carried out the first comparative calculations on enyne−allene cyclizations at the AM1/CI level of theory,[17] but it is clear from the overwhelming evidence in the literature and our own experience that semiempirical approaches do not handle singlet−triplet splittings well (for instance, the ΔE_{ST} of methylene is 30 kcal mol^{-1} at AM1; exptl value is 9.1 kcal mol^{-1}).[76,78] The first high-level *ab initio* study on the two cyclizations was reported by Engels and Hanrath,[27] who also disqualified AM1 as the method of choice for studying these two potential energy hypersurfaces. The authors used the CASSCF method with an active space of 10 electrons in 10 orbitals employing a 6-31G(d,f) basis set and compared these results with those obtained at B3LYP/6-31G(d) (*vide supra*). All structures were rather similar at both levels so that the time-saving DFT method seemed suitable for the geometries. However, keeping in mind what had been said above about the applicability of the CASSCF method and hybrid Hartree−Fock functionals such as B3LYP to biradical systems, it is not clear whether the agreement between the geometries at these two levels implies that the structures are close to experiment. As no structural experimental data are at hand for the structures of the parent system, the experimentally known activation and reaction energies for the Myers−Saito reaction[9] may be taken as a measure to assess the quality of a particular computational level. Engels and Hanrath find an activation barrier ($\Delta H^{\ddagger}_{0K}$) of 29 and 22 kcal mol^{-1} as well as a reaction enthalpy $\{\Delta H(R)_{0K}\}$ of +4 and −17 kcal mol^{-1}, at the CASSCF(10,10)/6-31G(d) and B3LYP/6-31G(d) levels of theory, respectively. As the experimental values are 21.8 ± 0.5 ($\Delta H_o^{\ddagger}$) and -15 ± 3 $\{\Delta H_o$-(R)$\}$,[8,9] or possibly 1−2 kcal mol^{-1} more positive,[98] it is clear that CASSCF does not yield a quantitatively correct picture of the energetics of the Myers−Saito reaction, despite the agreement in the structures (*vide infra*). Engels' and Hanrath's multireference CI (MR-CI+Q) Ansatz (using the CASSCF optimized geometries) does improve the energetics for the barrier (computed at this level as 25 kcal mol^{-1}) but overestimates the reaction enthalpy by 6−8 kcal mol^{-1}.[27] Since the barrier clearly is the most critical value to distinguish between the two reaction modes, namely to give the Myers−Saito or the Schmittel product, the MR CI+Q approach is quite suitable to study these systems but becomes quickly computationally intractable for larger structures.

Scheme 4. Ring-Closures of Carbocycles **12a−d** and Their Cyclization Products



The present study has several objectives. First of all, a suitable and feasible approach for computational studies on Myers−Saito as well as the Schmittel cyclizations should be identified. Since limited experimental data are available for the Myers−Saito reaction, we use these together with high-level single-point energies at the CCSD(T) and BCCD(T) levels with cc-pVDZ basis sets for the parent reactions to gauge the quality of other high-level methods and of the much less time-consuming BLYP/cc-pVTZ//BLYP/6-31G(d) computations.

Second, highly accurate barriers and reaction enthalpies for the title reactions of the parent systems are computed. High-level predictions for the heat of formation of the Myers−Saito (**8**) and Schmittel products (**10**) follow. While the first $\Delta H_f°$ is experimentally known, the error bars are relatively large (±3 kcal mol^{-1}); the $\Delta H_f°$ of **10** is, at least to our knowledge, unknown. Furthermore, the unpaired spin distributions of the key species are examined to aid in the prediction of their hydrogen abstraction ability; this also includes computations of the singlet−triplet separations of all biradicals under consideration in the present study.

Finally, to model and rationalize ring strain effects in enyne−allene analogues of the neocarzinostatin chromophore **1**, we used the carbocycles **12** to analyze the regioselectivity of the ring closure (Myers−Saito vs Schmittel) and the energetic consequences for the formation of the biradical intermediates (Scheme 4).

Computational Methods

Geometries of all stationary points were optimized using analytical energy gradients within density functional theory (DFT),[70−72] utilizing the BLYP (Becke−Lee−Yang−Parr) combination of gradient-corrected functionals,[89−91] as implemented in the Gaussian 94 program package.[99] For comparison, some computations were also carried out with Becke's three-parameter hybrid functional (B3)[90] and with Perdew's functional (BPW91).[100] Residual Cartesian and internal coordinate gradients for

(84) Sulzbach, H. M.; Platz, M. S.; Schaefer, H. F., III; Hadad, C. M. *J. Am. Chem. Soc.* **1997**, *119*, 5682−5689.
(85) Xie, Y.; Schreiner, P. R.; Schleyer, P. v. R.; Schaefer, H. F., III *J. Am. Chem. Soc.* **1997**, *119*, 1370−1377.
(86) Patterson, E. V.; McMahon, R. J. *J. Org. Chem.* **1997**, *62*, 4398−4405.
(87) Wong, M. W.; Wentrup, C. *J. Org. Chem.* **1996**, *61*, 7022−7029.
(88) Schaefer, H. F., III. *Science* **1986**, *231*, 1100−1107.
(89) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789.
(90) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372−1377.
(91) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098−3100.
(92) Martell, J. M.; Goddard, J. D.; Eriksson, L. A. *J. Phys. Chem. A* **1997**, *101*, 1927−1934.
(93) Scheiner, A. C.; Baker, J.; Andzelm, J. W. *J. Comput. Chem.* **1997**, *18*, 775−795.
(94) Lim, M. H.; Worthington, S. E.; Dulles, F. J.; Cramer, C. J. *Density Functional Calculations of Radicals and Diradicals*; in *Density-Functional Methods in Chemistry*; Laird, B. B., Ross, R. B., Ziegler, T., Eds.; American Chemical Society: Washington, DC, 1996; p 402.
(95) Schreiner, P. R.; Karney, W. L.; Schleyer, P. v. R.; Borden, W. T.; Hamilton, T. P.; Schaefer, H. F., III *J. Org. Chem.* **1996**, *61*, 7030−7039.
(96) Borden, W. T. Diradicals. In *The Encyclopedia of Computational Chemistry*; Schleyer, P. v. R., Allinger, N. L., Clark, T., Gasteiger, J., Kollman, P. A., Schaefer, H. F., III, Schreiner, P. R., Ed.; John Wiley & Sons: Chichester, 1998; pp 708−722.
(97) Borden, W. T. *Diradicals*; Wiley-Interscience: New York, 1982.
(98) Benson, S. W.; Garland, L. J. *J. Phys. Chem.* **1991**, *95*, 4915−4918.
(99) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian 94*, revision C.3; Gaussian, Inc.: Pittsburgh, PA, 1995.

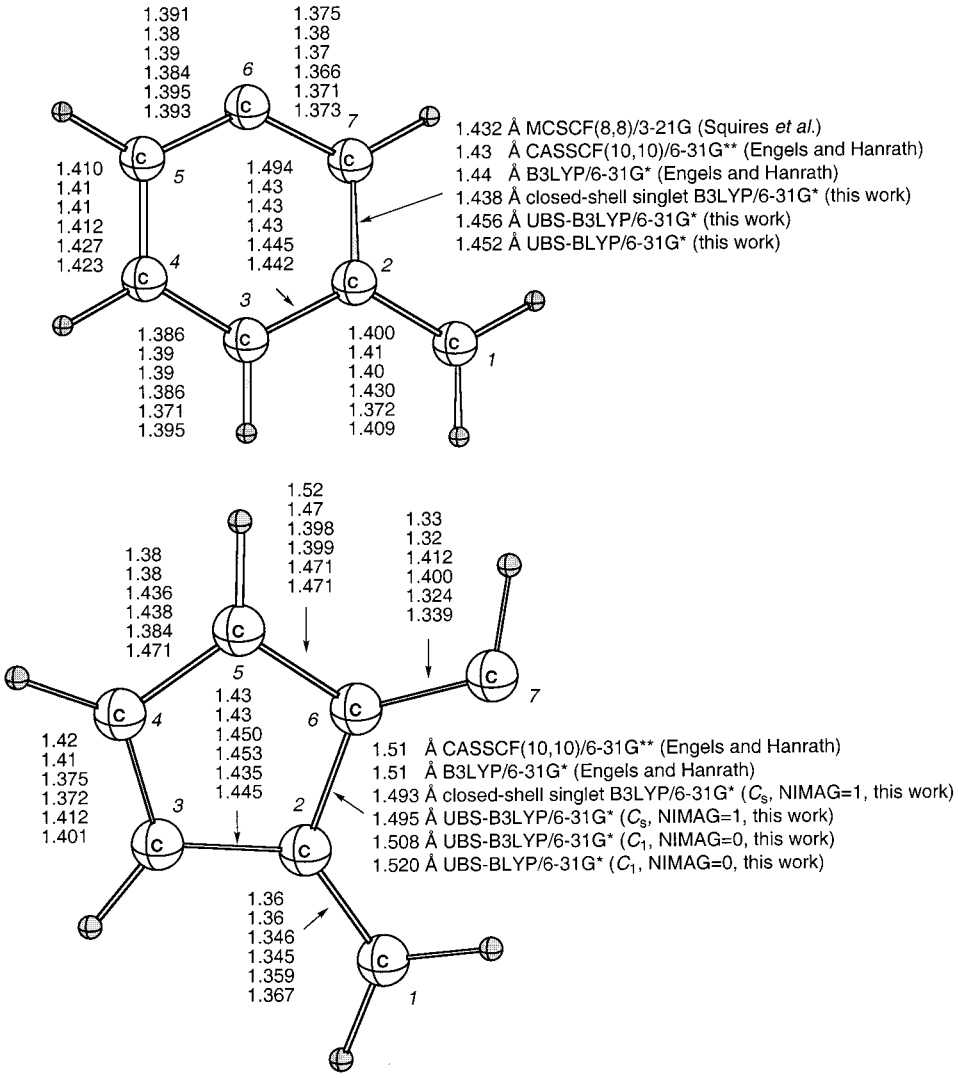
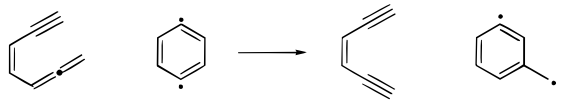


Figure 1. Comparison of the geometries of the Myers−Saito and Schmittel cyclization products at various levels of theory.

Table 1. Estimation of Systematic Errors for Bergman and Myers−Saito Cyclizations at Various Levels of Theory Using Eq 2 (Energies in kcal mol^{-1})



(2)

7 **15** **16** **8**

level of theory	ΔH_R (eq 2) = $\Delta H_{Bergman} - \Delta H_{Myers-Saito}$
MRSDCI/MIDI4[25]	22.7
B3LYP/6-31G(d)	36.1
BPW91/6-31G(d)	24.3
BPW91/cc-pVTZ//BPW91/6-31G(d)	24.8
BLYP/6-31G(d)	23.4
BLYP/cc-pVTZ//BLYP/6-31G(d)	23.7
CCSD(T)/cc-pVDZ//BLYP/6-31G(d)	34.9
BCCD(T)/cc-pVDZ//BLYP/6-31G(d)	22.5
experimental[12,49]	23.5 ± 3.5

Table 2. Singlet−Triplet Separations (ΔE_{ST}, *i.e.*, a Positive Value Denotes a Triplet Ground State) of Myers−Saito and Schmittel Cyclization Products of Enyne−Allenes at Various Levels of Theory[a]

level of theory	Myers−Saito product **8**	Schmittel product **10**
MCSCF(8,8)/cc-pVDZ// MCSCF(8,8)/3-21G[49]	−3.0	na
MR-CI+Q[27]	0.0	+5
B3LYP/6-31G(d)	+1.5	+3.1
BPW91/6-31G(d) + ZPVE	−1.1	+2.8
BPW91/cc-pVTZ//BPW91/6-31G(d) + ZPVE[b]	−1.0	+2.5
BLYP/6-31G(d) + ZPVE	−0.9	+2.0
BLYP/cc-pVTZ//BLYP/6-31G(d) + ZPVE[b]	−0.8	+1.7
CCSD(T)/cc-pVDZ//BLYP/6-31G(d) + ZPVE[b]	−15.1	+8.8
BCCD(T)/cc-pVDZ//BLYP/6-31G(d) + ZPVE[b]	−1.2	+2.9
experiment	−3.0[49]	na

[a] An unrestricted broken-spin symmetry wave function was used for the open-shell singlet structure; the triplet was computed with an unrestricted approach. [b] ZPVEs taken from BLYP/6-31G(d) frequency computations.

the stationary points were always less than 10^{-5} atomic units. Three basis sets were employed: 6-31G(d) for geometry optimizations as well as Dunning's correlation-consistent valence double-ζ (cc-pVDZ) and triple-ζ (cc-pVTZ) basis sets[101,102] for single-point energy evaluations using the BLYP/6-31G(d) geometries. Closed-shell singlet states were computed using restricted wave functions. For open-shell singlets (Myers−Saito and Schmittel products), we utilized unrestricted broken-spin symmetry wave functions (UBS). Triplet states were evaluated

(100) Perdew, J. P.; Burke, K.; Wang, Y. *Phys. Rev. B* **1996**, *54*, 16533−16539.

Table 3. Comparison of Computed Gibbs Free Activation and Reaction Enthalpies for the Myers−Saito and Schmittel (C^2-C^6 Cyclization of Enyene−Allenes) at 298 K at Various Levels of Theory[g]

	Myers−Saito cyclization[c]		Schmittel cyclization[c]	
level of theory	$\Delta^{\ddagger}G_{298K}$ (MS)	$\Delta_R G_{298K}$ (MS)	$\Delta^{\ddagger}G_{298K}$ (S)	$\Delta_R G_{298K}$ (S)
CASSCF(10,10)/6-31G(d)*[27]	29	4	37	18
MR CI+Q[27 a,b]	25	−21[f]	35	12
BPW91/6-31G(d)	18.0	−13.8	28.6	9.2
BPW91/cc-pVTZ//BPW91/6-31G(d)	19.6	−9.4	30.2	16.1
BLYP/6-31G(d)	20.2	−7.8	31.5	14.2
BLYP/cc-pVTZ//BLYP/6-31G(d)[d]	22.7	−2.1	34.4	19.3
CCSD(T)/cc-pVDZ//BLYP/6-31G(d)[d]	22.2	−24.3	35.0	17.3
BCCD(T)/cc-pVDZ//BLYP/6-31G(d)[d]	22.2	−11.9	34.8	10.0
experiment	21.8 ± 0.8[e]	−15 ± 3[e]	na	na

[a] Using an Huzinaga's (9s5p) AO DZ basis set in Dunning's [4s2p] contraction with d functions added ($a_d = 0.7$) on carbon and a (4s) AO → [2s] contracted basis for hydrogen.[124] [b] These values are not ZPVE or thermally corrected (*i.e.*, ΔH). [c] Reactants and products were computed with restricted wave functions (unrestricted wave functions gave identical geometries for these structures); products were computed with broken-spin symmetry wave functions (see text). [d] Thermal corrections from BLYP/6-31G(d) vibrational frequency calculations. [e] Reference 9. Myers *et al.* note that the heat of formation for the parent enyne−allene may have to be corrected downward by 1−2 kcal mol^{-1} so that $\Delta G_{MS}^{\ddagger}$ and ΔG_{MS} are more likely around 23.3 ± 1 and −13.5 ± 4 kcal mol^{-1}, respectively. [f] A much larger ANO basis set gives −18 kcal mol^{-1}.[27] [g] Experimental values were derived from the heats of formation of the respective singlet ground states.

with an unrestricted approach (U). All stationary structures were identified as minima (number of imaginary frequencies (NIMAG) = 0) or transition structures (NIMAG = 1) by computation of analytic vibrational frequencies, which were also used to compute zero-point vibrational energies (ZPVE) and thermal enthalpy contributions ($\Delta H_{298K} - \Delta H_{0K}$).

For the most critical structures, we evaluated single-point energies utilizing the coupled-cluster with single and double excitations plus perturbatively included triplet excitations Ansatz, CCSD(T)[58,59,61,63,103] as well as the Brueckner-doubles (BD)[64] coupled cluster approach, BCCD(T)[65−69,104,105] with Hartree−Fock reference wave functions. All coupled-cluster calculations were carried out with the cc-pVDZ basis set.

Results and Discussion

Choice of Theoretical Approach. As pointed out in the Introduction, the choice of level of theory to study the title reactions is not straightforward. Pure DFT approaches are superior to hybrid Hartree−Fock functionals, and they seem to offer a reasonable compromise to study biradical systems such as the Bergman cyclization,[36,37,40,44,45,94] but the treatment of the open-shell Myers−Saito (**8**) and Schmittel (**10**) products requires some explanation and justification. Since both **8** and **10** are σ,π-biradicals with small ΔE_{ST}'s (*vide infra*) and are planar or nearly so, an unrestricted broken-spin symmetry (UBS) wave function where

$$\mathrm{HOMO}_{\alpha} = \frac{\mathrm{HOMO} + \mathrm{LUMO}}{\sqrt{2}} \quad \text{and}$$

$$\mathrm{HOMO}_{\beta} = \frac{\mathrm{HOMO} - \mathrm{LUMO}}{\sqrt{2}} \qquad (1)$$

should be a good approximation of the true wave function.[34,45] A well-written detailed discussion of this approach may be found in Cramer's work on *para*-benzyne chemistry.[45] The expectation values for the spin operator $\langle S^2 \rangle$ for Slater determinants for such wave functions is probably not very meaningful due to apparent singlet−triplet mixing; we note that restricted wave functions for **8** and **10** are unstable with respect to symmetry breaking.

A close inspection of the geometries (Figure 1) and energies of **8** and **10** shows that Engels' and Hanrath's B3LYP/6-31G(d) structure is slightly different from ours; the absolute energy is given as −270.22878 au, we compute −270.22907 au at UBS-B3LYP (C_1). While the numerical difference is likely to be a rounding error, the disagreement in the geometries is small (only found for the C5−C6 bond length) but troublesome. This problem may also be related to the symmetry labels of the triplet states of **8** and **10** which Engels and Hanrath denote as $^3A'$, whereby we find, in agreement with Squires *et al.*,[41,106] that the triplet of **8** should be denoted $^3A''$. By analogy, the open-shell singlet and triplet states of **8** and **10** are also of A″ symmetry. Although the B3LYP structure of **8** *apparently* is planar (C_s), the energy in this symmetry is different (UBS-B3LYP/6-31G(d) = −270.18963) from the one of the C_1 structure. The symmetric/asymmetric structures of **10** obtained at various levels show a similar pattern. Although the structure of **10** is almost perfectly planar (with the largest dihedral angle of 0.005°), a computation in C_s symmetry gives a transition structure at UBS-B3LYP/6-31G(d) with an imaginary frequency of 625*i* cm^{-1}! Hence, the symmetric UBS-B3LYP/6-31G(d) wave functions clearly suffer from symmetry breaking[107] and are therefore unsuitable to study the title reactions.

Most of the above problems are not encountered when pure DFT wave functions are used (we have tested BLYP and BPW91, *vide infra*). This conclusion, reached independently by one of us,[36,37] Chen *et al.*,[44] and Cramer *et al.*,[40,45,46,79,94,108] seems generally to be true for biradicals as well as carbenes. As Cramer pointed out, it is not the case that the HF-DFT functionals are intrinsically flawed but it is likely that the added HF character decreases the quality of the Kohn−Sham solutions for these electronically difficult systems.[45]

The high degree of multireference character (in the classical HF formalism) also implies that a high-level coupled-cluster wave function may suffer from symmetry breaking due to the fact that the reference orbitals may not be optimal for the state under consideration. As noted in the Introduction and suggested

(101) Dunning, T. H., Jr. Basis Sets: Correlation-Consistent. In *The Encyclopedia of Computational Chemistry*; Schleyer, P. v. R., Allinger, N. L., Clark, T., Gasteiger, J., Kollman, P. A., Schaefer, H. F., III, Schreiner, P. R., Eds.; John Wiley & Sons: Chichester, 1998; pp 88−115.
(102) Dunning, T. H., Jr. *J. Chem. Phys.* **1989**, *90*, 1007−1023.
(103) Raghavachari, K.; Trucks, G. W.; Pople, J. A.; Head-Gordon, M. *Chem. Phys. Lett.* **1989**, *157*, 479−483.
(104) Chiles, R. A.; Dykstra, C. E. *J. Chem. Phys.* **1981**, *74*, 4544−4556.
(105) Stanton, J. F.; Gauss, J.; Bartlett, R. J. *J. Chem. Phys.* **1992**, *97*, 5554−5559.
(106) Wenthold, P. G.; Wierschke, S. G.; Nash, J. J.; Squires, R. R. *J. Am. Chem. Soc.* **1993**, *115*, 12611−12612.
(107) Carbó, R. *Self-Consistent Field: Theory and Application*; Elsevier: Amsterdam, 1990.
(108) Cramer, C. J.; Truhlar, D. G.; Falvey, D. E. *J. Am. Chem. Soc.* **1997**, *119*, 12338−12342.

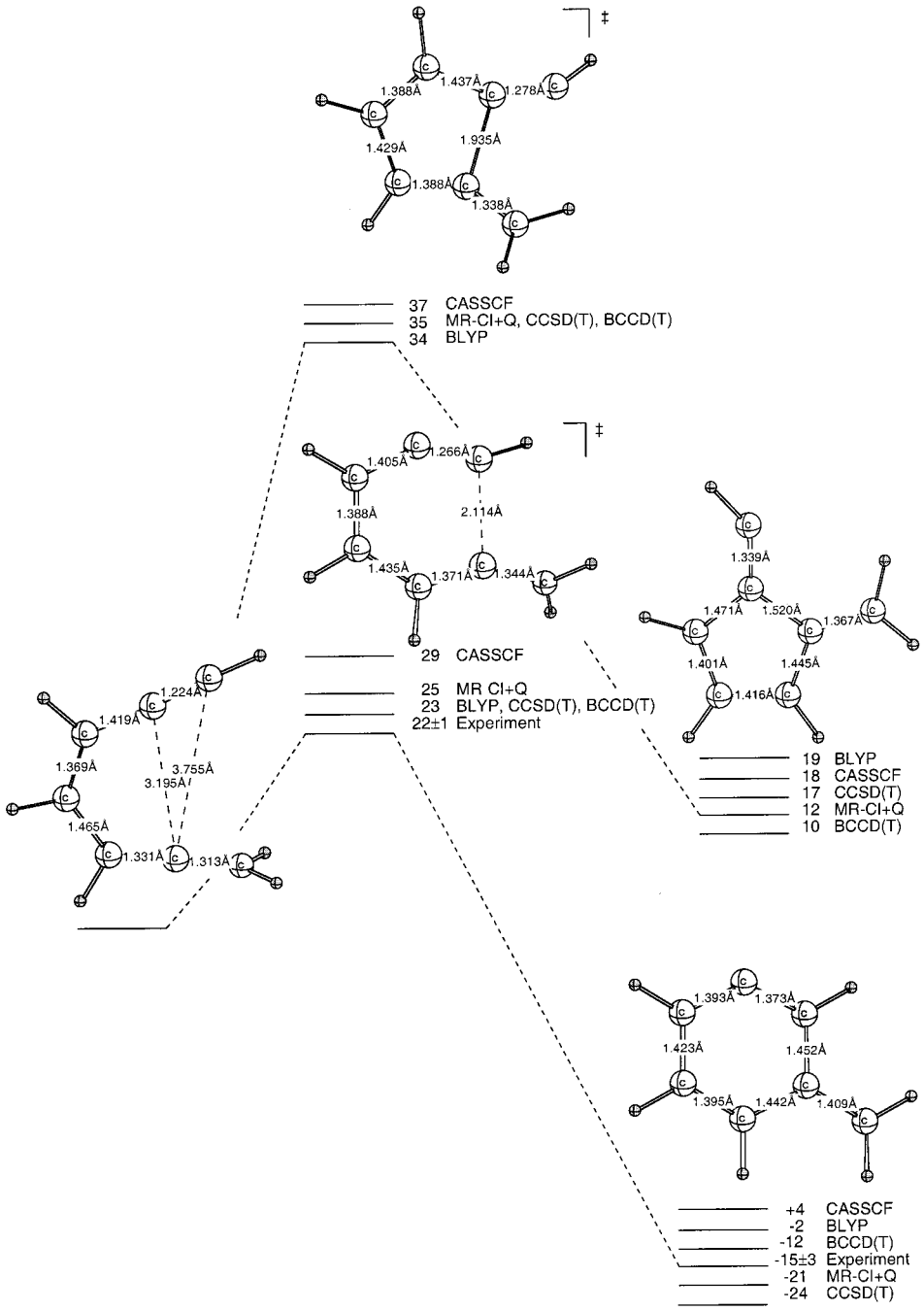


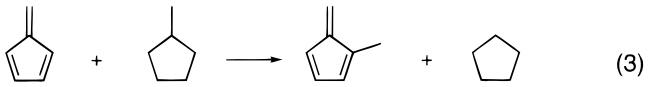
Figure 2. Comparison of the relative energies of the Myers−Saito and Schmittel cyclizations at various levels of theory.

by Cramer,[45] the use of Brueckner orbitals[64] may salvage this approach for low-symmetry systems. The BD orbitals are determined in the presence of the correlation perturbation so that the amplitudes of the single excitations vanish.[58] As a consequence, the resulting Brueckner determinant is generally more stable than other HF-based references.

This line of arguments is strongly supported by several aspects of the computations on the parent system. First of all, we aimed at finding out whether the chosen (BLYP) approach is systematically correct for evaluating the experimentally known reaction enthalpies for the Bergman and Myers−Saito reaction, *i.e.*, if absolute computed errors in the isodesmic eq 2 cancel (Table 1). While all chosen high-level *ab initio* methods and BLYP reproduce the experimental value within its error bars, B3LYP clearly fails in this respect (error about 14 kcal mol^{-1}), due to the reasons noted above. Second, we also find that the CCSD(T) results are far inferior to BCCD(T) due to the problems that arise with computing the energy of *para*-benzyne (**15**) and the Myers−Saito product (**8**). As Cramer pointed out, this is not to say that CCSD(T) is inferior to BCCD(T) for most chemical structures where results at these two levels usually agree within 0.1 kcal mol^{-1}.[45]

A second way of judging the quality of the BLYP and the BCCD(T) approaches is to compare the ΔE_{ST}'s at these levels to Engels' and Hanrath's high-level MR-CI+Q values (Table 2). The authors find that the ΔE_{ST} of **8** is practically zero, which explains the trouble with symmetry breaking at B3LYP and CCSD(T). While the B3LYP/6-31G(d) result is just acceptable for this property when the structures are computed without symmetry constraints, the CCSD(T)/cc-pVDZ//BLYP/6-31G(d) ΔE_{ST} is surprisingly large in error (about 12 kcal mol^{-1}). As suggested, the situation is much better with BCCD(T), which gives a ΔE_{ST} of −1.2 kcal mol^{-1}, *i.e.*, also a singlet ground state for **8**, in agreement with experiment and MCSCF computa-

Table 4. Determination of the Heat of Formation of 2-Methylfulvene via Eq 3 to Derive the Heat of Formation of **6**[b]

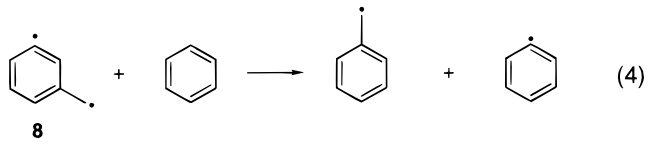


(3)

ΔH_o at	$\Delta_R H_o$	$\Delta H_f°$ methylfulvene
BLYP/cc-pVTZ[a]	−2.0	44.7
CCSD(T)/cc-pVDZ[a]	−1.2	45.5
BD(T)/cc-pVDZ[a]	−1.3	45.4

[a] Using the geometries and ZPVE corrections at BLYP/6-31G(d); for all energies see the Supporting Information. [b] Absolute energies in −au, ΔH values in kcal mol^{-1}. The experimental heats of formation in kcal mol^{-1} are 53.6 (fulvene), −25.3 (methylcyclopentane), and −18.4 (cyclopentane)[125].

Table 5. Comparison of the Computed and Experimentally Derived Heat of Formation of **8** via Eq 4[b]



(4)

ΔH_o at	$\Delta_R H_o$	$\Delta H_f°$ (**8**)
BLYP/cc-pVTZ[a]	+0.6	107.0 ± 2
CCSD(T)/cc-pVDZ[a]	+17.1	90.2 ± 2
BD(T)/cc-pVDZ[a]	+0.6	107.0 ± 2
exptl.	−4.4	103 ± 3[106]

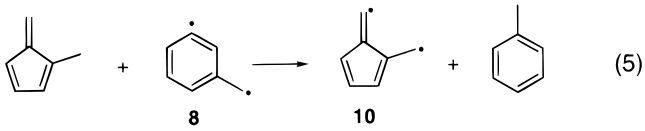
[a] Using the geometries and ZPVE-corrections at BLYP/6-31G(d). [b] Absolute energies in −au, ΔH values in kcal mol^{-1}. The experimental heats of formation in kcal mol^{-1} are 19.7 (benzene[125]), 79.1 ± 2 (phenyl radical[106]), and 48 ± 2 (tolyl radical[126]).

tions (without considering dynamic electron correlation) (Table 2).[106] The pure DFT results (BLYP and BPW91) agree with the BCCD(T) and MR-CI+Q results within about 1 kcal mol^{-1}, also suggesting a singlet ground state. Since even a full configuration interaction treatment of methylene with a TZ2P basis set[109] still deviates by about 1.7 kcal mol^{-1} from experiment,[110−112] we do not expect the MR-CI+Q value to be the final answer, but it is likely to be the closest to experiment among all the chosen methods. Hence, in agreement with Engels and Hanrath, the singlet−triplet separation of **8** is rather small.

The Schmittel product **10**, on the other hand, has a triplet ground state with an ΔE_{ST} of 3−4 kcal mol^{-1}. As a consequence of this sizable separation, the discrepancy between CCSD(T) and BCCD(T) becomes somewhat smaller (about 6 kcal mol^{-1}) for **10** than for **8**.

Energies and Structures of the Parent System (Table 3, Figure 2). As found for the transition state for the Bergman cyclization,[35,37,45,113] the transition structures for the two cyclization pathways virtually display no biradical character. This is evident from the fact that the energies computed at restricted and unrestricted levels of theory are essentially identical and that the spin operator expectation value for unrestricted wave functions is virtually zero. Hence, the experimental barrier (*via* $\mathbf{TS_{MS}}$) for the Myers−Saito cyclization should be well reproduced at the levels of theory employed here. Myers remarked[9] that the heat of formation of the parent enyne−allene (**7**, 118 kcal mol^{-1}) may have be corrected downward by 1−2 kcal mol^{-1} [98] so that the activation barrier for the Myers−Saito cyclization should be about 23 kcal mol^{-1}, a value which is very well reproduced at MR CI+Q, BLYP, CCSD(T), and BCCD(T). The CASSCF approach overshoots by about 6 kcal mol^{-1} due to the neglect of dynamic electron correlation. The agreement of the different levels for the Schmittel cyclization barrier (*via* $\mathbf{TS_S}$; experimentally not known, computed as 29−35 kcal mol^{-1}) is equally good, whereby CASSCF is at the high end. Our best prediction for this barrier is 35 kcal mol^{-1}.

Table 6. Determination of the Heat of Formation of **10** via Eq 5[b]

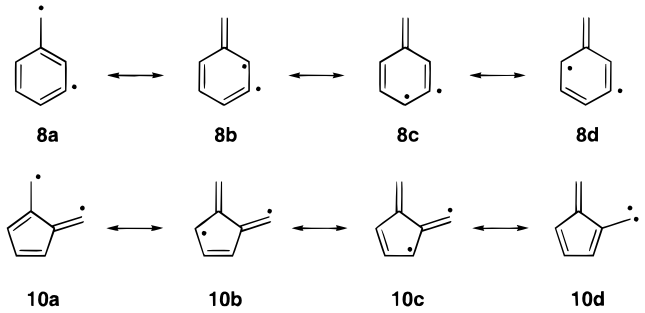


(5)

ΔH_o at	$\Delta_R H_o$	$\Delta H_f°$ (**10**)
BLYP/cc-pVTZ[a]	−9.7	126.7
CCSD(T)/cc-pVDZ[a]	+12.3	148.7
BD(T)/cc-pVDZ[a]	−7.4	129.0

[a] Using the geometries and thermal corrections from vibrational frequency computations at BLYP/6-31G(d); see Table 4. [b] Absolute energies in −au, ΔH values in kcal mol^{-1}. The experimental heats of formation in kcal mol^{-1} are 103 ± 3 (**8**), 12.0 (toluene), and −18.4 (cyclopentane).

Scheme 5. Spin Resonance Structures for Myers−Saito and Schmittel Cyclization Biradical Products



The energies of the open-shell products are much more difficult to compute (*vide supra*); the experimental heat of formation of **8** also has a relatively large error bar (±3 kcal mol^{-1}),[106] which adds to the 1−2 kcal mol^{-1} error for **7**. Hence, the experimental reaction enthalpy for the Myers−Saito cyclization is in the range of −13 ± 4 kcal mol^{-1}. A comparison shows (Figure 2) that the Myers−Saito cyclization at CASSCF is endothermic (+4 kcal mol^{-1}), in contrast to experiment and all other levels of theory; the MR CI+Q reaction enthalpy is highly exothermic (−21 kcal mol^{-1}, with the CASSCF geometries). CCSD(T) is equally bad due to the problems associated with computing the energy of **8**. While the BCCD(T) results agree nicely with the experimental value (within about 1 kcal mol^{-1}), BLYP/cc-pVTZ is not exothermic enough. This may be a problem associated with this particular basis set which was developed for electron correlation methods and not for DFT;[101,102] a similar pattern can be found throughout this study, unless isodesmic reactions are used. The combination of cc-pVXZ basis sets in conjunction with DFT approaches should therefore be used with caution.

The reaction enthalpies for the Schmittel reaction computed at the various levels center around 14 ± 5 kcal mol^{-1}, whereby BCCD(T) lies at the lower and CASSCF as well as BLYP at the high end. Our best prediction for the cyclization enthalpy of the Schmittel reaction is about 10 kcal mol^{-1}.

(109) Sherrill, C. D.; Van Huis, T. J.; Yamaguchi, Y.; Schaefer, H. F., III. *J. Mol. Struct. (THEOCHEM)* **1997**, *400*, 139−156.
(110) Davidson, E. R.; Feller, D.; Phillips, P. *Chem. Phys. Lett.* **1980**, *76*, 416−417.
(111) Jensen, P.; Bunker, P. R. *J. Chem. Phys.* **1988**, *89*, 1327−1332.
(112) Handy, N. C.; Yamaguchi, Y.; Schaefer, H. F., III. *J. Chem. Phys.* **1986**, *84*, 4481−4484.
(113) Galbraith, J. M.; Schreiner, P. R.; Harris, N.; Wei, W.; Wittkopp, A.; Shaik, S. *Chem. Eur. J.*, in press.

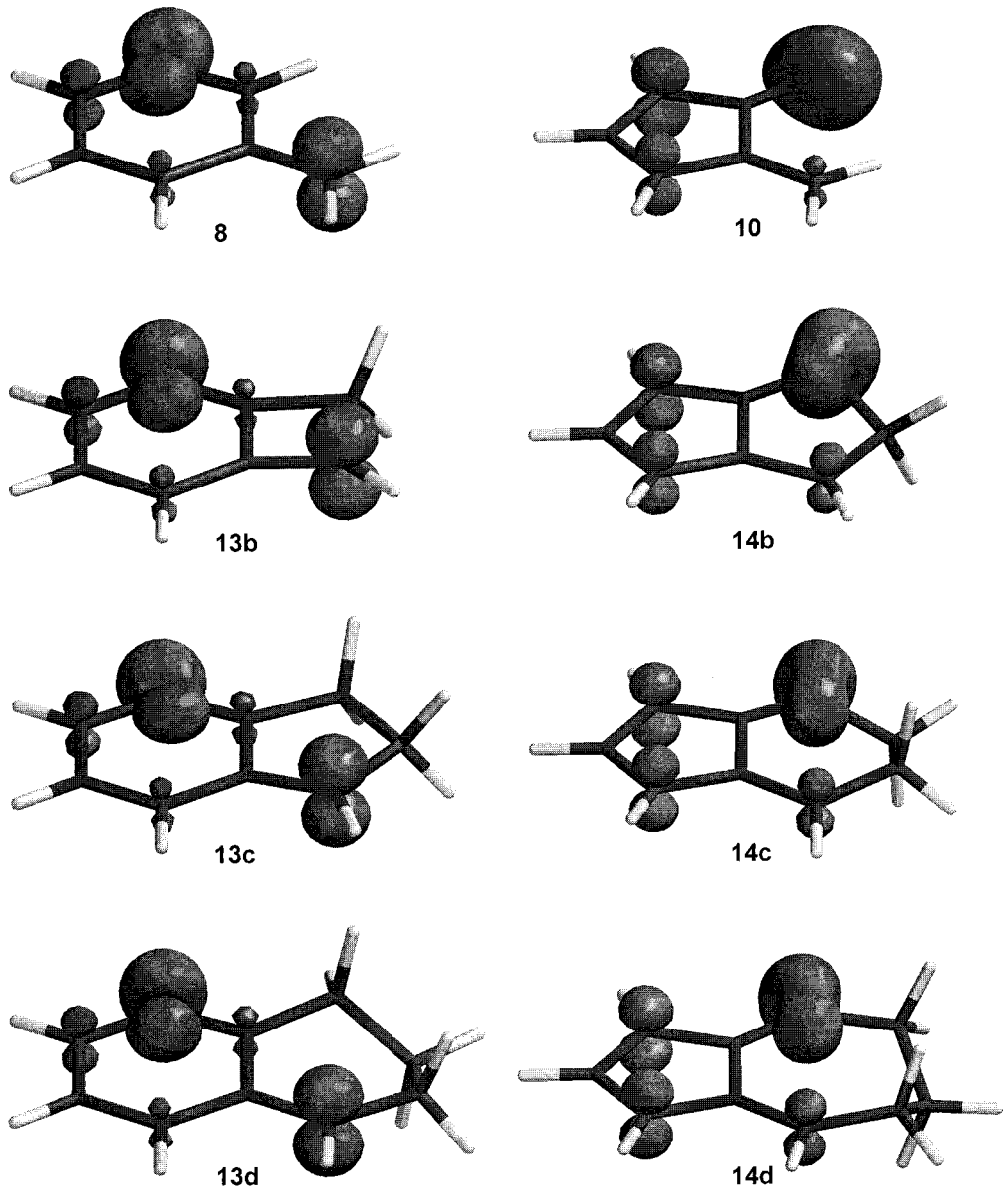


Figure 3. Open-shell spin densities of the Myers−Saito and Schmittel cyclization biradical products. The depicted spin density coeffiecients were computed for the triplet states. As the singlet−triplet separations are very small (see text), these spin densities are also a very good qualitative approximation of the open-shell singlet spin distributions.

The heat of formation for **10** has, to the best of our knowledge, not been determined experimentally or computationally. This may be due to the fact that while the heat of formation of fulvene is known (53.6 kcal mol^{-1}),[114] the $\Delta H_f°$ of 2-methyl fulvene is not. Hence, we derived this value through isodesmic eq 3 (Table 4). It is encouraging to see that the deviation of the heat of formation determined at BLYP and the coupled cluster levels of theory is rather small (0.8 kcal mol^{-1}) due to systematic error cancellation. Using 45.4 kcal mol^{-1} as the $\Delta H_f°$ of 2-methyl fulvene, we set out derive the heat of formation of **10** employing the $\Delta H_f°$ of **8** (103 ± 3 kcal mol^{-1}). To convince ourselves that the isodesmic approach works well also for these species, we first derived the experimentally known heat of formation of **8** by eq 4 (Table 5).[106] Although the agreement between theory and experiment is just satisfactory, the derived value of 107 kcal mol^{-1} for the $\Delta H_f°$ of **8** sheds new light on the finding of Wenthold *et al.* that the bond energy additivity calculations, which give $\Delta H_f°$ (**8**) = 107.6 ± 1.7 kcal mol^{-1}, do not agree with the experimental value.[49] As Wenthold's MCSCF calculations also predict a somewhat larger value (105−106 kcal mol^{-1}), it is likely that the ±3 kcal mol^{-1} error bar has a positive sign and that the $\Delta H_f°$ of **8** should be slightly higher.

Equation 5 (Table 6) was then used to derive the heat of formation of **10** in a similar fashion. Hence, our best estimate for $\Delta H_f°$ (**8**) is 129 ± 4 kcal mol^{-1}. With the two heats of formation for **8** and **10** at hand, we compute the difference of the two cyclization reactions as about 26 ± 4 kcal mol^{-1}, which agrees well with the computed values at BLYP (21 kcal mol^{-1}) and BCCD(T) (22 kcal mol^{-1}). The MR-CI+Q value (33 kcal mol^{-1}) is relatively large in error; CASSCF (14 kcal mol^{-1}) and CCSD(T) (42 kcal mol^{-1}) are not acceptable. Taking all of the above computations and experiments including their error bars into account, our best estimate for the reaction enthalpy of the Myers−Saito reaction is −14 kcal mol^{-1}.

An important unanswered question is where the spin densities in **8** and **10** are located, *i.e.*, which of the spin-resonance structures (**8a**−**d** and **10a**−**d**, Scheme 5) are important. This,

(114) Roth, W. R.; Adamczak, O.; Breuckmann, R.; Lennartz, R.; Boese, R. *Chem. Ber.* **1991**, *124*, 2499−2521.

Table 7. Gibbs Free Activation and Uncorrected Reaction Enthalpies[a] for the Cyclization of Cyclic Enyne−Allenes **12a**−**d** in kcal mol^{-1} at BLYP/6-31G(d) (PG = Point Group; NImag = Number of Imaginary Frequencies)

ring size	structure	ΔH	ΔH_0	ΔH_{298K}	ΔG_{298K}	PG/NImag
7	**12a**	0.0	0.0	0.0	0.0	C_1/0
	TS$_{MS}$12a	10.0	8.8	8.6	9.0	C_1/1
	13a	9.7	9.0	9.0	9.0	C_1/0
	TS$_{S}$12a	25.4	23.9	23.7	24.0	C_1/1
	14a	14.3	14.1	14.1	14.0	C_1/0
8	**12b**	0.0	0.0	0.0	0.0	C_1/0
	TS$_{MS}$12b	18.4	17.3	17.0	17.8	C_1/1
	13b	3.8	3.5	3.2	3.8	C_s/0
	TS$_{S}$12b	15.7	14.8	14.3	15.2	C_1/1
	14b	2.0	2.1	1.7	2.6	C_1/0
9	**12c**	0.0	0.0	0.0	0.0	C_1/0
	TS$_{MS}$12c	14.7	13.8	13.4	14.2	C_1/1
	13c	−11.8	−11.9	−12.3	−11.8	C_s/0
	TS$_{S}$12c	12.8	11.8	11.4	12.3	C_1/1
	14c	4.1	3.8	3.3	4.2	C_1/0
10	**12d**	0.0	0.0	0.0	0.0	C_1/0
	TS$_{MS}$12d	16.6	15.9	15.4	16.6	C_1/1
	13d	−12.6	−12.3	−12.9	−11.5	C_1/0
	TS$_{S}$12d	23.0	21.8	21.4	22.4	C_1/1
	14d	7.2	6.8	6.3	7.3	C_1/0

[a] The enthalpies may be corrected downward by the error for the parent reactions at this level (6 and 4 kcal mol^{-1} for the Myers−Saito and Schmittel cyclizations, respectively).

together with the ΔE_{ST}, determines the hydrogen-abstracting ability of these biradicals in DNA cleavage reactions.[47] Since the singlet−triplet separations are relatively small (*vide supra*), the coefficients of the distributed spin densities of the open-shell singlets and triplets are qualitatively very similar (Figure 3 depict the triplet spin densities for **8** and **10**).[115]

While the σ-radical site located in an sp^2 orbital is highly localized and cannot interact with the bonds or other orbitals, the π-radical site shows the typical delocalization as found in, *e.g.*, benzylic or allylic systems. The consequences for **8** are not dramatic because the aromatic benzene electron sextet does not effectively interact with the benzylic radical; spin resonance depiction **8a** followed by **8c** are the most appropriate representations of the spin density for the Myers−Saito cyclization product. The Schmittel product, on the other hand, shows a rather different pattern where **10a** is the least important as it does not account for the true distribution of the π-radical density, which is best presented by **10c**. These findings are also supported by the bond lengths of optimized **10** (Figure 1), where the C1−C2 bond (1.367 Å) is shorter than the C2−C3 bond (1.445 Å). Significant resonance is further indicated by the deviation of the fact that the C2−C3, C3−C4, C4−C5, and C5−C6 bond lengths are between single and double bonds. This also explains why the difference in the heats of formation between **8** and **10** (26 kcal mol^{-1}) is less than expected if **10** were not stabilized. The theoretical difference should be about 13 + 21 = 33 kcal mol^{-1} for benzylic and aromatic stabilization of **8**[116,117] but is smaller because **10** also benefits from allylic resonance. Hence, while **8** is best described as a benzyl/σ-diradical, **10** has an allyl/σ-structure.

Effect of Ring Size on Cyclization (Table 7, Figure 4). Given the excellent agreement of BLYP with experiment and BCCD(T) for the cyclization barriers and the sizable deviations in the reaction enthalpies for the parent reactions, the following sections will argue quantitatively for the barriers but will refrain to relative energy comparisons for the reaction enthalpies. As noted above, the BLYP/cc-pVTZ single-point energies do not necessarily improve the results; as we attempt to draw conclusions which may be verified by experiment, we use the BLYP/6-31G(d) Gibbs free enthalpies in the following discussion. Of course, one could correct for the likely to be systematic error in computing the reaction free enthalpies for the parent systems at this level (about 6 and 4 kcal mol^{-1} for the Myers−Saito and Schmittel cyclizations, respectively). However, the qualitative changes are, apart from the seven-membered ring system, rather minor so that the overall picture will not change.

As found for the Bergman cyclization,[36,37,44] ring strain has a large effect on the cyclization barriers and enthalpies for the Myers−Saito and Schmittel reactions. In turn, this is a way of adjusting (a) the barriers for synthetic antitumor pharmacophors based on cyclic enyne−allenes and (b) the ratio of Schmittel over Myers−Saito cyclization. Since the Bergman and Schmittel cyclizations are endothermic, the strain of the products should dominate the barriers for the ring closures of cyclic reactants; the exothermic Myers−Saito reaction should be sensitive to ring strain effects of the reactants.[118]

First of all, we find that all cyclic enyne−allenes studied here (7−10-membered rings, **12a**-**d**) have smaller ring-closure barriers than the parent systems due to the inherent strain of the starting materials. The Myers−Saito cyclizations of enyne−allenes **12a**−**d** are endothermic for the small rings **12a** as well as **12b** and about equally exothermic for **12c** and **12d**. The enthalpies for the Schmittel cyclizations of **12a**−**d** parallel these findings: the cyclizations are less than or as endothermic as the parent reaction, and the reverse barriers are considerably smaller (9−14 kcal mol^{-1} vs about 24 kcal mol^{-1} for the parent systems). Temperature and entropic effects generally lower the cyclization barrier by about 1 kcal mol^{-1} but have virtually no effect of the reaction enthalpies (Table 7). Hence, these reactions are not likely to be highly temperature dependent, in agreement with Engels' and Hanrath's findings for the parent system.[27]

As expected, the cyclization reactions of the highly strained seven-membered ring enyne−allene **12a** are highly unfavorable. Since the reverse barrier is negligible, the Myers−Saito cyclization of **12a** via **TS$_{MS}$12a** will not occur. The corresponding Schmittel reaction has a considerably lower barrier (24 vs 34 kcal mol^{-1}) and reaction enthalpy (14 vs 19 kcal mol^{-1}) as the parent system. Hence, if cyclization occurs and if suitable hydrogen donors are present, the seven-membered enyne−allene **12a** (if it can be prepared) should give Schmittel products only. However, a close inspection of the nonplanar product structure (Figure 4) indicates that it is a closed-shell cyclopropylidene derivative with a long C—C bond rather than an open-shell biradical;[75,77,119−122] we were unable to locate the structure of the latter state.

The eight-membered enyne−allene **12b** has a significantly lower barrier (15 vs 34 kcal mol^{-1}) and a much less endothermic reaction enthalpy (3 vs 19 kcal mol^{-1}) for the Schmittel reaction, making it the thermodynamically most favorable one in this series. Since the Myers−Saito cyclization for this ring size shows about the same endothermicity (4 kcal mol^{-1}) but a higher barrier (18 kcal mol^{-1}), the Schmittel reaction should be the favored cyclization mode for the eight-membered monocyclic enyne−allene **12b**. These findings can be rationalized by the

(115) *Wavefunction I*, 5.1.1, Spartan; Wavefunction, Inc.: Irvine, 1998.
(116) Roth, W. R.; Ruf, G.; Ford, P. W. *Chem. Ber.* **1974**, *107*, 48−52.
(117) Schleyer, P. v. R.; Jiao, H. *Pure Appl. Chem.* **1996**, *68*, 209−218.
(118) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334−338.
(119) Xantheas, S.; Elbert, P.; Ruedenberg, K. *Theor. Chim. Acta* **1991**, *78*, 365−395.
(120) Xantheas, S.; Valtazanos, P.; Ruedenberg, K. *Theor. Chim. Acta* **1991**, *78*, 327−363.
(121) Valtazanos, P.; Elbert, S. T.; Xantheas, S.; Ruedenberg, K. *Theor. Chim. Acta* **1991**, *78*, 287−326.

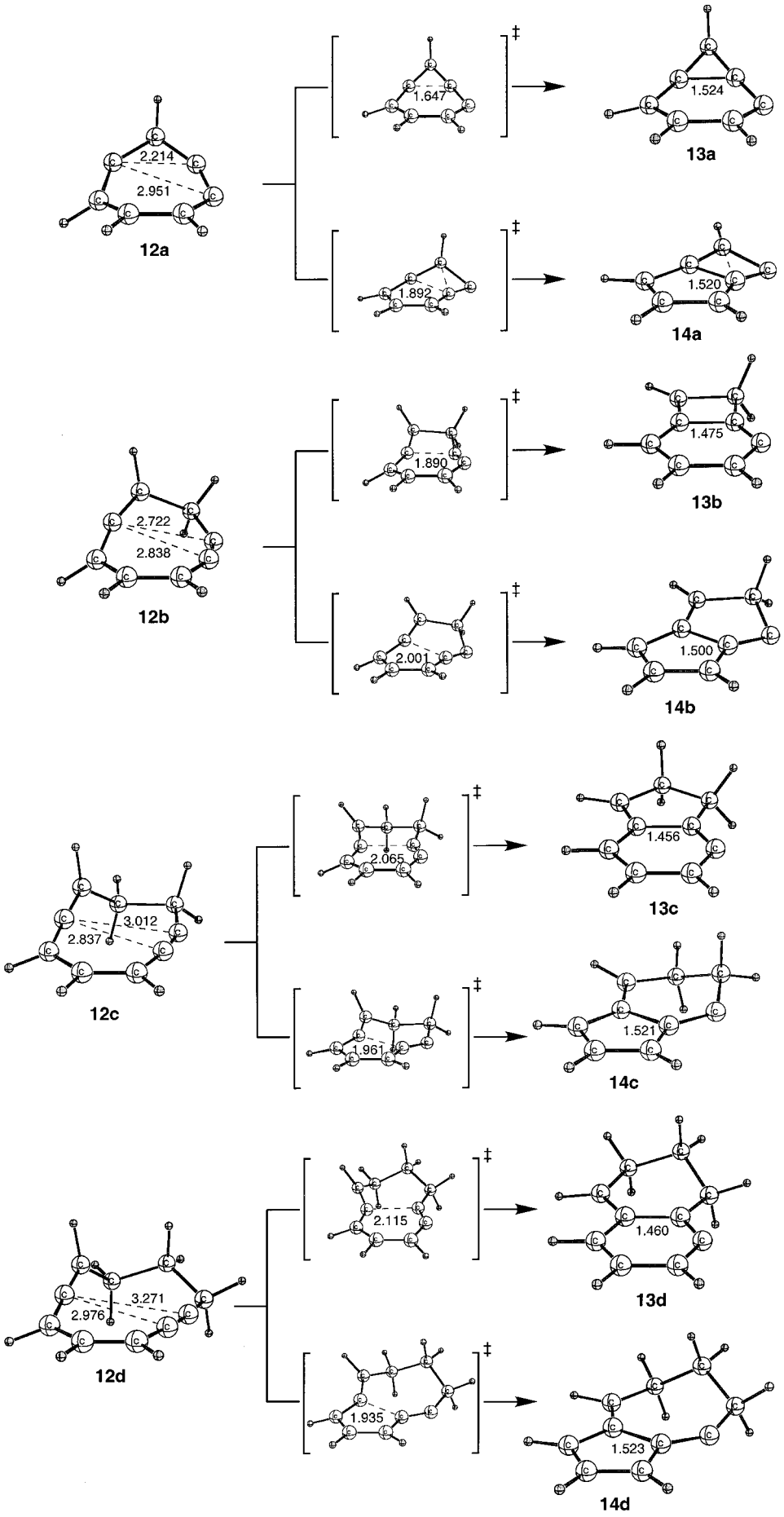


Figure 4. BLYP/6-31G(d) geometries of the Myers−Saito and Schmittel cyclizations of monocyclic enyne−allenes.

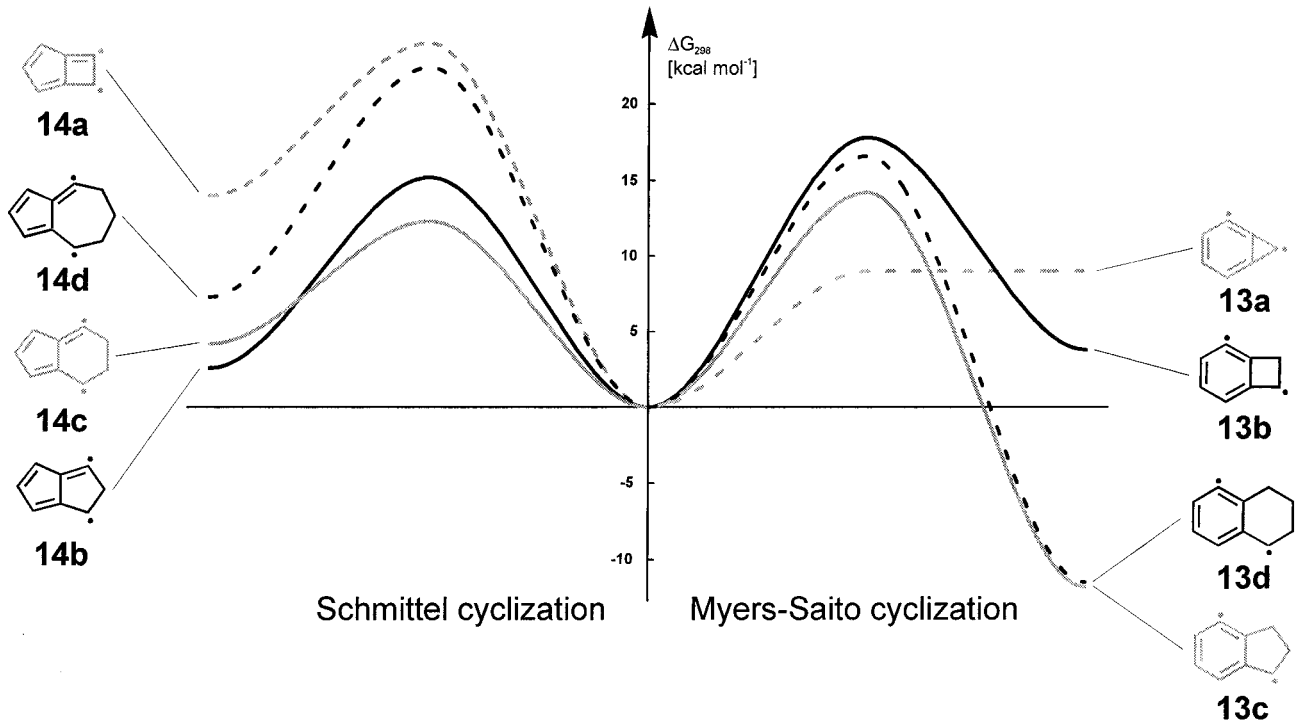


Figure 5. Comparison of the barriers and enthalpies of the Myers−Saito and Schmittel cyclizations of monocyclic enyne−allenes **12a**−**d** and the parent system.

difference in olefin strain energies for the cyclobutene (31 kcal mol^{-1}) and cyclopentene (7 kcal mol^{-1})[123] moieties in the biradical products **13b** and **14b**, respectively.

While the energetics of the larger rings slowly return to what was found for the parent reaction, it is quite remarkable that the nine-membered ring, which is also a part of neocarzinostatin **1** and the hydrocarbon **6**, is associated with the lowest barriers to cyclization for both reactions (14 and 12 kcal mol^{-1}; Table 7 and Figure 5)! Moreover, the Myers−Saito reaction enthalpy for this ring size is the lowest of all enyne−allenes considered in the present study. Part of the driving force for the cyclizations of **12c** originates from the small olefin ring strain in the cyclopentene and cyclohexene moieties formed in the two reactions. Another reason is the short distance between the reacting centers in the ring which is considerably longer in the parent system (3.195 and 3.755 Å in **7** vs 2.837 and 3.012 Å in **12c** for the Schmittel and Myers−Saito pathways, respectively), resulting in higher cyclization activation energies for **7**. The Schmittel cyclization barrier increases much more than the Myers−Saito barrier on going to the 10-membered ring, favoring the latter transformation. Hence, ring strain effects and distances of the reacting carbon centers not only are highly important in these cyclization reactions but may also be used to design enyne−allene containing antitumor antibiotics which cyclize at physiological or other specific temperatures.

As found for the parent system, the ΔE_{ST}'s are very small for the cyclic biradicals (Table 8); the Myers−Saito products have a slight preference for a singlet ground state, while the Schmittel products favor the triplet state. The hydrogen-abstracting ability and hence antitumor reactivity of both biradical types should therefore be rather high.[47] The triplet (and hence qualitatively very similar open-shell singlet) spin densities are also depicted in Figure 3. The conjugation of the π-spin densities in **13b**−**d** and **14b**−**d** is more apparent than that in **8** and **10**.

Table 8. Singlet−Triplet Separations (ΔE_{ST}, *i.e.*, a Positive Value Denotes a Triplet Ground State) of Myers−Saito and Schmittel Cyclization Products of Monocyclic Enyne−Allenes at Two Levels of Theory[a]

level of theory	BLYP/6-31G(d)	BLYP/cc-pVTZ//BLYP/6-31G(d)[b]
13a	−4.3[c]	−4.8[c]
13b	−0.8	−0.7
13c	−0.8	−0.7
13d	−0.8	−0.8
14a	−8.3[c]	−8.9[c]
14b	2.3	1.4
14c	−0.4	0.5
14d	1.8	1.5

[a] An unrestricted broken-spin symmetry wave function was used for the open-shell singlet structures; the triplets were computed with an unrestricted approach. [b] ZPVEs taken from BLYP/6-31G(d) frequency computations. [c] No open-shell singlet was located; see text.

Conclusions

In the present work, we examined in detail the Myers−Saito and C^2−C^6 cyclizations (termed "Schmittel cyclization") of parent and monocyclic enyne−allenes employing various high-level *ab initio* and density functional theory approaches. As was found for the related Bergman cyclization of enediynes, pure (nonhybrid) DFT methods (*e.g.*, BLYP and BPW91) are qualitatively suitable to study these types of systems. Hybrid methods such as B3LYP are larger in error for energies due to Hartree−Fock mixing; symmetry-breaking may also become a problem at this level of theory. Correlation-consistent basis sets do generally not improve but sometimes even worsen the results.

(122) Valtazanos, P.; Ruedenberg, K. *Theor. Chim. Acta* **1991**, *78*, 397−416.
(123) Schleyer, P. v. R.; Williams, J. E.; Blanchard, K. R. *J. Am. Chem. Soc.* **1970**, *92*, 2377−2386.
(124) Dunning, T. H., Jr. *J. Chem. Phys.* **1970**, *53*, 2823−2833.
(125) Lias, S. G.; Bartmess, J. E.; Liebman, J. F.; Holmes, J. L.; Levin, R. D.; Mallam, W. G. *J. Phys. Chem. Ref. Data* **1988**, *17* (Suppl. 1), 1−872.
(126) McMillen, D. F.; Golden, D. M. *Annu. Rev. Phys. Chem.* **1982**, *33*, 493−532.

Hence, these basis sets should be used with caution in connection with DFT.

The cyclization barriers are exceptionally well reproduced relative to experimental data owing to the single-reference character of the corresponding transition structures. The reaction enthalpies generally are too positive using DFT approaches, but are in better agreement with experimental data for the Myers−Saito reaction than the much more demanding CASSCF approach.

Results close to experiment for the parent system can be obtained employing high-level coupled-cluster methods in conjunction with Brueckner orbitals {BCCD(T)} and correlation-consistent basis sets (cc-pVDZ). The CCSD(T) method performs similarly but suffers from near-degeneracy for the Myers−Saito product giving unacceptably low energies.

The computed {by means of an isodesmic equation at BCCD(T)/cc-pVDZ//BLYP/6-31G(d)} enthalpy of formation ($\Delta H_f°$) of the Myers−Saito product (107 ± 4 kcal mol^{-1}) compares relatively well to the experimental value (103 ± 3 kcal mol^{-1}) where an upward correction within the error bars seems indicated. Using the same approach the $\Delta H_f°$ of the Schmittel product is predicted to be 129 ± 4 kcal mol^{-1}. A spin-density analysis shows that the Myers−Saito product is a benzyl/σ-diradical, whereas the Schmittel biradical has an allyl/σ-structure.

To qualitatively understand the effect of ring strain on the two reaction modes, we used BLYP/6-31G(d) to compute the cyclizations of monocyclic enyne−allenes (ring sizes = 7−10 carbons). All cyclization reactions have smaller barriers and reaction enthalpies relative to the parent system due to inherent ring strain in the starting materials; temperature dependencies and entropic effects are rather small for these reactions. The seven-membered system is unlikely to give cyclization products due to small reverse barriers for ring opening. The formation of the Schmittel product is kinetically slightly favored for the eight-membered enyne−allene. The Myers−Saito cyclization of the nine-membered ring is associated with the smallest reaction barrier and the highest exothermicity. A downward correction of 4−6 kcal mol^{-1} for the reaction enthalpies taking into account the computational error for the parent systems at BLYP/6-31G(d) does not alter the qualitative conclusions drawn here but may be used for more accurate quantitative predictions.

The singlet−triplet separations of all cyclization products are rather small (1 kcal mol^{-1}) with a slight preference for singlet and triplet ground states for the Myers−Saito and Schmittel products, respectively. Hence, the hydrogen-abstracting ability of such cyclic systems is expected to be rather high.

Acknowledgment. This paper is dedicated to the memory of Robert R. Squires. We acknowledge support from the Fonds der Chemischen Industrie (Liebig-Fellowship for P.R.S.), the Deutsche Forschungsgemeinschaft (Schr 597/1-1 and 597/3-1). We are grateful to Prof. A. de Meijere for his support, the Höchstleistungsrechenzentrum Stuttgart (HLRS), and the RRZN Hannover for generous allotments of computer time. We thank A. Wittkopp for his help.

Supporting Information Available: Tables of all calculated energies (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA991282+