Monocyclic Enediynes: Relationships between Ring Sizes, Alkyne Carbon Distances, Cyclization Barriers, and Hydrogen Abstraction Reactions. Singlet−Triplet Separations of Methyl-Substituted *p*-Benzynes

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Received October 15, 1997. Revised Manuscript Received January 29, 1998

Abstract: The Bergman-type cyclizations of parent, 2,3-dimethyl, and monocyclic (ring sizes = 7−12) enediynes were studied in detail at the Becke−Lee−Yang−Parr (BLYP) density functional (DFT) level with 6-31G* as well as 6-311+G** basis sets for geometry optimizations and relative energy evaluations, respectively. Pure DFT methods work reasonably well for these reactions; the errors are somewhat larger (ca. 3−7 kcal mol^{-1}) than for the much more time-consuming complete active space (CASPT2) and coupled-cluster [CCSD(T)] (both in error by ca. 2 kcal mol^{-1}) methods with high-quality basis sets. The hybrid method B3LYP is unsuitable for this type of chemistry (errors of 14−20 kcal mol^{-1}). The singlet−triplet energy separations (ΔE_{ST}) for *p*-benzynes are underestimated systematically by about 2 kcal mol^{-1} at BLYP; the ΔE_{ST} of 2-methyl-*p*-benzyne (−3.1 kcal mol^{-1}) is close to that of *p*-benzyne (−3.8 kcal mol^{-1}, i.e., singlet ground state) but the 2,3-dimethyl-*p*-benzyne ΔE_{ST} is only −0.6 kcal mol^{-1} due to singlet destabilization (methyl repulsion). 2,3-Dialkyl-*p*-benzynes thus have nearly degenerate singlet and triplet states. While we find that there is clearly no predictive relationship between the alkyne carbon distance (*d*) and the cyclization activation enthalpy ($\Delta H^{\ddagger}$) for monocyclic enediynes, Nicolaou's empirically determined "critical range" of 3.31−3.2 Å, where spontaneous cyclization should occur at room temperature, should be extended to 3.4−2.9 Å. However, ring strain effects may become more important than distance arguments. Dimethyl substitution increases the endothermicity of the Bergman reaction (by about 12 kcal mol^{-1}). The cyclization of a nine-membered enediyne is only mildly endothermic; larger rings give larger endothermicities. The formation of final products via double hydrogen abstraction from 1,4-cyclohexadiene is highly exothermic. The exothermicity decreases with increasing ring size due to unfavorable H···H repulsion in the products.

Introduction

While the Bergman cyclization[1] of (*Z*)-hexa-1,5-diyn-3-enes (**1**, enediynes) is driven thermodynamically by subsequent formation of two new C−H bonds (products **3**), the pharmacological activity[2−5] of cyclic enediynes (**4**) such as Calicheamicin (**7**)[6,7] or Dynemicin (**8**) is also related to the changes in ring strain upon cyclization (aromatization, to **2**, Scheme 1).[8−13] In fact, the ring closure in enediyne-carrying drugs complexed to the minor groove of DNA is triggered by subtle structural perturbations.[8] The resulting aromatic singlet biradical is the active species which stepwisely abstracts two hydrogen atoms from DNA phosphodiester strands,[3] ultimately leading to cell death. Hence, enediynes are highly promising pharmacophors, but reactivity control is still a problem. It is therefore highly desirable to determine the factors which govern the cyclization step.

Nicolaou *et al.* suggested[13,14] that the distance (*d*, Scheme 1) of the acetylene carbons forming the new bond may be related to the activation barrier for ring closure. More specifically, spontaneous Bergman cyclization should occur at room temperature when *d* is in the critical range of 3.31−3.20 Å.[8,13] In contrast, both Magnus *et al.*[15,16] and Snyder[11,12] argued that differential molecular strain in the educts and transition states is the commanding element for ring closure. This was substantiated by experimental observations (activation energies

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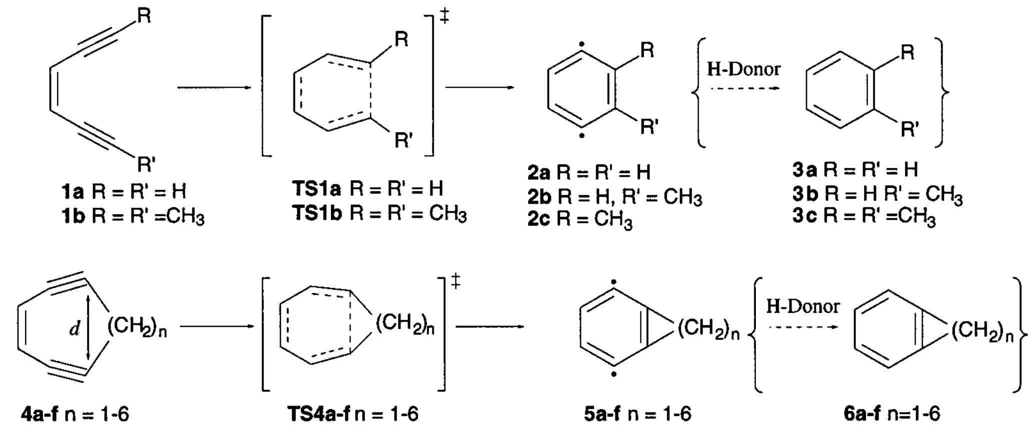
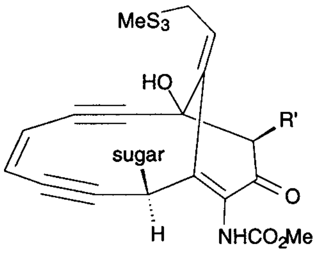
S0002-7863(97)03591-9 CCC: $15.00

Scheme 1





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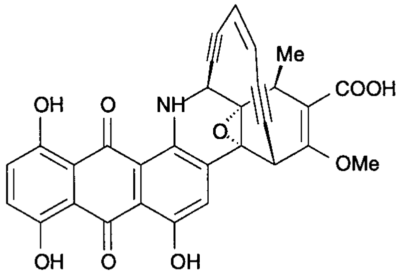

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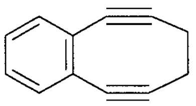

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and X-ray structures of a few C_9–C_{12} cyclic enediynes) and by empirical computations.

There are several studies attempting to clarify the relationship between *d* and cyclic enediyne cyclization as well as the ground-state energy differences, but transition structures for any other but the smallest enediynes were never computed.[17–22] It was recognized, however, that "*the reactivity of a given enediyne compound toward Bergman cycloaromatization is determined by the free energy* [enthalpy] *of activation* ($\Delta G^{\ddagger}$)".[17] In the only *ab initio* study analyzing a 10-membered-ring cyclic enediyne, geometries were optimized at the Hartree–Fock level using the STO-3G minimal basis set, leading to geometries where multiple bonds are too short (*vide infra*).[17] Product stabilities were evaluated by the hypothetical reaction of the enediyne precursor with H_2, but it is not clear if this reaction is directly relevant to benzyne radical abstraction chemistry.

Hence, without the transition structures and activation energies for Bergman cyclization of monocyclic enediynes at hand, it is not clear whether there is a clear-cut relationship between *d* and the ease of cyclization. One of the goals of this paper was therefore the examination of the effects determining the energy changes during enediyne ring closure (considering *d*) and to see if the barriers can be predicted based upon the energies of the starting materials (the approaches by Magnus et al.[15,20] as well as Snyder[11,12]) or the products. The results can then guide lower level computations on much larger systems.

The modeling of large—ideally the experimental—enediynes is currently only possible with molecular mechanics,[13,21,22] semiempirical,[11,12,20,23] or lowest level *ab initio* methods.[17] However, due to the underlying theory, these approaches cannot be used to compute accurate transition structures and activation energies; much higher level treatments are needed to include the effects of electron correlation explicitly.[19,24–27]

Density functional theory (DFT), on the other hand, may offer a suitable compromise, but it is not clear if the quantum mechanically difficult treatment of the biradical species—here the *p*-benzynes **2**—can be handled properly with DFT methods. While hybrid Hartree–Fock DFT methods such as B3LYP do not, although not thoroughly tested, seem to perform well for computing the heat of formation of *p*-benzyne **2a**,[26] "pure" DFT treatments, e.g., BPW91, leave a mixed impression.[27] Our experience and other's generally very positive experience with DFT computations for carbene geometries and energies, which can be considered as one-center biradicals, prompted us to apply this attractive approach to enediyne chemistry as well.[28–33]

The present report is the first comprehensive study on a series of cyclic hydrocarbon enediynes to show that the cyclization

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barrier clearly depends on the ground-state energy differences of the products. In a methodological survey, it is also demonstrated that the Bergman reaction, a difficult case for quantum mechanical methods due to the multireference character of the intermediate biradicals,[25] can be described qualitatively with pure density functional theory.

Computational Methods

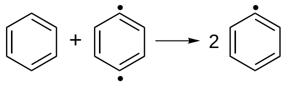
The geometries of all stationary points were optimized using analytical energy gradients within DFT,[34] utilizing the BLYP (Becke−Lee−Yang−Parr) functional,[35,36] as implemented in the Gaussian 94 program package.[37] Residual Cartesian and internal coordinate gradients for the stationary points were always less than 10^{-5} au. Two basis sets were employed: 6-31G* for geometry optimization and 6-311+G** for final energy evaluations using the BLYP/6-31G* geometries. As the systems under consideration here are quite large, we were encouraged by the good performance of the BLYP/6-311+G**//BLYP/6-31G* approach (see discussion below) for the Bergman reaction (most other high-level *ab initio* methods would be prohibitively time-consuming). Electronic singlet states were computed using restricted wave functions; triplets states were computed with an unrestricted approach. For the latter case, the spin-operator expectation values ($\langle S^2 \rangle$) did not exceed 2.010. Broken-spin symmetry wave functions for the singlets gave about 5 kcal mol^{-1} lower energies but were highly spin contaminated.[52]

Results and Discussion

Choice of Theoretical Approach. There is good agreement that the experimental activation barrier for ring closure of **1a** is 28−32 kcal mol^{-1} and that the heat of formation ($\Delta H_\mathrm{f}^\circ$) of **2a** is 138.0 ± 1 kcal mol^{-1} [38] (137.8 ± 2.9 kcal mol^{-1} [39]). Provided somewhat larger error bars, theory can reproduce the best experimental values.[19,24,26,27] The experimentally well-established reaction enthalpy ($\Delta H_{\mathrm{R},298\mathrm{K}}$: 8.5 ± 1.1[38] and 8.3 ± 2.9 kcal mol^{-1} [39]) is still somewhat controversial theoretically: 3.5 ± 2.0[26] and 10.0 kcal mol^{-1} [19] are noted in earlier papers, but the most recent and probably most accurate computation at CASPT2/aANO gives 8.7 kcal mol^{-1},[27] in excellent agreement with experiment.

To check the validity of the theoretical approach used here, the performance of various methods was first evaluated with isodesmic equation (1) (Table 1), following the approach by Wierschke *et al.*[40] Since the dominant configurations of the biradical singlets **2** and **5** as well as in the corresponding transition structures (*vide infra*) should yield rather similar densities, we assumed that a nonhybrid DFT method like BLYP should describe these species rather well.[27] Exceptionally good performance of DFT methods for carbenes has been documented.[28−33] In particular, singlet−triplet energy separations (ΔE_ST) agree quite well with experiment, despite the multireference character of the singlet species. It has been argued that the insensitivity of density functional methods toward multireference wave functions is due to the fact the electron density, and not the wave function itself, is the decisive quantity,[28,29] in other words, "*the extent to which multiple configurations having the same symmetry mix into the final state representation*".[31] Since different spin states and configurations often produce similar densities, DFT approaches can work well.

Table 1. Evaluation of Theoretical Methods for the Bergman Reaction (ΔH_R) Using Isodesmic Reaction 1; Heat of Formation ($\Delta H_\mathrm{f}^\circ$) for *p*-Benzyne (**2a**) at 298 K in kcal mol^{-1} [a]



(1)

2a

level	ΔH_R	$\Delta H_\mathrm{f}^\circ$(**2a**)	ΔE_ST(**2a**)[e]
expt	4.7	137.3 ± 3.3;[39] 138.0 ± 1.0[38]	−3.8 ± 0.5[50]
CASSCF/aANO[b]	3.0	139.6	−3.8[27]
CASPT2(8,8)/aANO[b]	4.4	138.2	−5.8[27]
BPW91/cc-pVTZ[27]	−3.6	146.2	+1.6[27]
CCSD(T)/cc-pVTZ[c]	5.4	137.2	−2.3[27]
B3LYP/6-31G*	−14.6	157.3	+13.2
B3LYP/6-311+G**[d]	−12.6	155.3	+11.1
BLYP/6-31G*	−4.2	146.9	+0.1
BLYP/6-311+G**[d]	−2.6	145.3	−1.5

[a] Using the following heats of formation in kcal mol^{-1}: benzene = 19.7; phenyl radical = 81.2.[39,49] [b] aANO = averaged atomic natural orbital bases; this energy evaluation used CASSCF(8,8) geometries. For details, see refs 26 and 27. [c] Energy extrapolated as E[CCSD(T)/cc-pvTZ] ≈ E[CCSD/cc-pVTZ] + E[CCSD(T)/cc-pVDZ] − E[CCSD/cc-pVDZ].[27] [d] Geometries, thermochemical corrections, and ZPVE obtained with a 6-31G* basis set. [e] Singlet−triplet energy separation computed as $\Delta E_\mathrm{ST} = \Delta E(\text{singlet}) - \Delta E(\text{triplet})$; i.e., a negative value indicates a singlet ground state.

Table 1 demonstrates that these arguments favoring DFT only hold for the pure density functional method BLYP, which agrees reasonably well with experiment. Cramer *et al.* have shown very recently that the nonhybrid functional BPW91 also reproduces both the heat of formation of **2a** and the ΔE_ST satisfactorily.[27] The B3LYP performance, however, is rather poor for the reaction enthalpy (ΔH_R) and the so derived heat of formation of *p*-benzyne (**2a**), $\Delta H_\mathrm{f}^\circ$. As demonstrated by the large deviations in the ΔE_ST (see below) at B3LYP, the errors in ΔH_R and $\Delta H_\mathrm{f}^\circ$ are clearly associated with an incorrect description of singlet **2a** caused by the hybrid part of B3LYP. The error at our reference level (BLYP/6-311+G**/BLYP/6-31G*) is around 7 kcal mol^{-1} for $\Delta H_\mathrm{f}^\circ$ (**2a**) and ca. 2 kcal mol^{-1} for ΔE_ST (**2a**). The error for the latter quantity is similar to the errors found in the ΔE_ST's of the carbenes studied at density functional levels of theory.[28−30] More importantly, our reference level also gives the correct sign for the ΔE_ST of **2a**, which has a singlet ground state (i.e., $\Delta E_\mathrm{ST} < 0$).[40] This is one of the few cases where BLYP is clearly superior to B3LYP in determining a reaction barrier or a ΔE_ST.

As expected for true multireference approaches, the complete active space method without (CASSCF) and with perturbative inclusion of electron correlation (CASPT2) perform quite well. As Cramer *et al.* pointed out,[27] the earlier CASPT2/aANO

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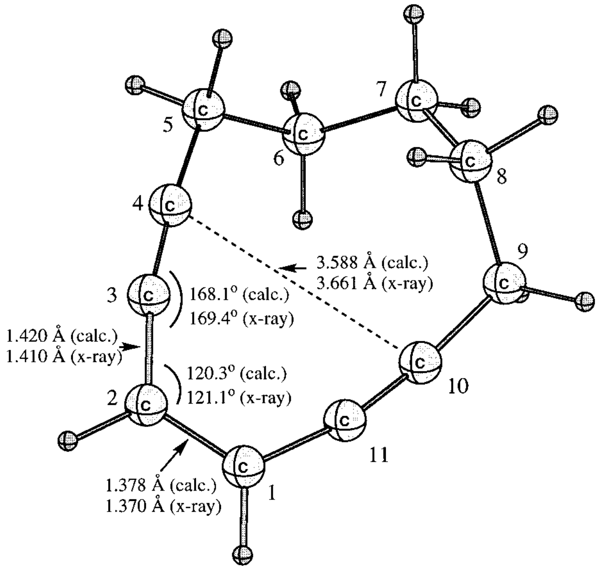
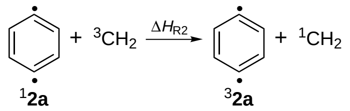


Figure 1. Comparison of computed (BLYP/6-31G*) and experimentally determined geometrical parameters for **4e**.

Table 2. Singlet−Triplet Separations (ΔE_{ST}) of *p*-Benzynes (**2a**) and Methylene as Well as the Reaction Enthalpy of Eq 2 {$\Delta H_{R2} = \Delta E_{ST}(CH_2) - \Delta E_{ST}(\mathbf{2a})$} in kcal mol^{-1}



(2)

level	$\Delta E_{ST}(CH_2)$	ΔE_{ST}(**2a**)	ΔH_{R2}
BLYP/6-31G* + ZPVE[a]	11.6	0.1	11.5
BLYP/6-311+G**// BLYP/6-31G* + ZPVE[a]	10.3	−1.5	11.8
expt	9.1 ± 0.1[51]	−3.8 ± 0.5[50]	12.9

[a] ZPVE (unscaled) at 298 K.

results for $\Delta H_f°$ reported by Lindh and Schütz[26] are in error because the authors seem to have used the enediyne instead of the *p*-benzyne absolute energy in some of the energy evaluations. The single-reference coupled cluster method with perturbatively included triple excitations {CCSD(T)} performs very well but is somewhat prone to errors for near-degeneracy cases (part of the correlation energy of **2** and **5** will be neglected).[19]

The BLYP/6-31G* geometries are very similar to those found with CASSCF[25] and CCSD(T).[19] The computed structure for **4e** compares favorably with its C_2-symmetric X-ray structure (Figure 1).[13] The HF/STO-3G geometries reported earlier for **4d** are—not unexpectedly—rather poor (enediyne moiety numbering as for **4e**, Figure 1, BLYP/6-31G* vs HF/STO-3G[17]): C1−C2, 1.38 vs 1.33 Å; C2−C3, 1.42 vs 1.46 Å; C3−C4, 1.23 vs 1.18 Å; ∠C1−C2−C3, 119.5° vs 118.0°.

Singlet−Triplet Separations (ΔE_{ST}). The singlet−triplet gaps are generally difficult to compute accurately due to the necessity to include both dynamic and static electron correlations, which is particularly important for singlets **2**.[53a] As mentioned above, however, DFT gives reasonable ΔE_{ST}'s for carbenes; moreover, the errors using different basis sets are comparable, allowing corrections to the ΔE_{ST}'s.[28−30] The electronic structures of biradicals such as *p*-benzynes and carbenes are related, and one would expect a systematic error for the ΔE_{ST}'s of *p*-benzynes. This issue is addressed in Table 2 (eq 2), where the ΔE_{ST} for **2a** is evaluated against that of methylene at two levels of theory. First of all, one should note that the ΔE_{ST} of methylene is 10.3 kcal mol^{-1} at the highest level of theory, in good agreement with experiment (9.1 kcal mol^{-1}) and in better agreement than a full configuration interaction (FCI) treatment with an even larger TZ2P basis set (11.1 kcal mol^{-1}).[41] The ΔE_{ST} of **2a** is, however, too small by 2.3 kcal mol^{-1} at our reference level. BPW91/cc-pVTZ performs slightly worse in giving an error of 5.4 kcal mol^{-1} (Table 1).[27] As discussed above, the error at B3LYP/6-311+G**/B3LYP/6-31G* is much larger, namely, 16.9 kcal mol^{-1}, due to unfavorable Hartree−Fock mixing. Equation 2 (Table 2) also shows that the errors in computing the ΔE_{ST}'s of **2a** and methylene appear to be systematic: the computed reaction enthalpies (ΔH_{R2}) are almost the same at the two levels considered; they only deviate by about 1 kcal mol^{-1} from experiment. Thus, the ΔE_{ST} of **2a** may be corrected by a constant; this was done for **2b** and **2c** (Table 3).

Table 3. Singlet−Triplet Separations (ΔE_{ST}) of Parent and Methyl-Substituted *p*-Benzynes (Monomethyl **2b**, Dimethyl **2c**) in kcal mol^{-1}, Corrected ($\Delta E_{ST,corr}$) for the Error in Computing the ΔE_{ST} for **2a** at the Corresponding Level Relative to the Experimental ΔE_{ST} (−3.8 ± 0.5 kcal mol^{-1} [50])

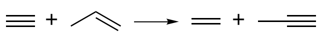
	ΔE_{ST}		$\Delta E_{ST,corr}$	ΔE_{ST}	$\Delta E_{ST,corr}$
	2a	**2b**	(**2b**)	(**2c**)	(**2c**)
BLYP/6-31G* + ZPVE[a]	0.1	0.6	−3.3	3.0	−0.7
BLYP/6-311+G** + ZPVE[a]	−1.5	−0.8	−3.1	1.7	−0.6

[a] Geometry and ZPVE (unscaled at 298 K) at BLYP/6-31G*.

How does alkyl substitution in **2a** influence ΔE_{ST}? At first glance, there should be little change since the in-plane (of the benzene ring) singly occupied sp^2 hybrid orbitals bearing the unpaired electron spin cannot interact effectively with an alkyl substituent in positions 2 and 3 (Figure 2). This assumption holds true for monomethyl-substituted **2b**, which has a ΔE_{ST} (−3.1 kcal mol^{-1}, corrected, Table 3) similar to that of **2a** (−3.8 kcal mol^{-1}). Disubstitution, however, destabilizes the singlet state to give a ΔE_{ST} of −0.6 kcal mol^{-1} (corrected, Table 3) for **2c**, due to increased repulsion of the two methyl groups. The C3−C2−CH$_3$ angle has to widen to decrease the methyl group repulsion: from 115° in ^{1}**2a** to 117.3° in ^{1}**2c** (Figure 2). As this change in geometry from the parent to the dimethyl case is smaller for the triplet (121.0° in ^{3}**2a** to 122.1° in ^{3}**2c**, Figure 2), the ΔE_{ST} becomes less negative. Thus, the singlet−triplet states in 2,3-dialkyl-substituted monocyclic enediynes become essentially degenerate. Sterically demanding substitution at both C2 and C3 should further destabilize the singlets.

Cyclization Reactions. As noted above, the geometries of the enediyne cyclization reactions are rather well reproduced at our reference level—theory vs experiment: 28.4 vs 28.2 kcal mol^{-1} [38] for TS1a; 25.0 vs 23.8[13] and 24.0 kcal mol^{-1} for TS4d.[18,20] Thus, the effect of *d* (see above) on the activation energies can be probed in detail qualitatively and quantitatively for the first time.

Enediynes **1a** and **1b** display almost the same *d* (Δd = 0.023 Å) and should thus have similar cyclization barriers if there was a linear relationship between *d* and $\Delta H^{‡}$. However, their difference in activation enthalpies is 7.2 kcal mol^{-1}! This is primarily due to the fact that methyl groups stabilize acetylenic bonds (in **1b**) much more than olefinic bonds (developed partially in TS1b): the reaction enthalpy of the isodesmic equation (3) is −10.8 kcal mol^{-1}. This alkyl substitution effect



(3)

is further supported by the difference in reaction enthalpies for

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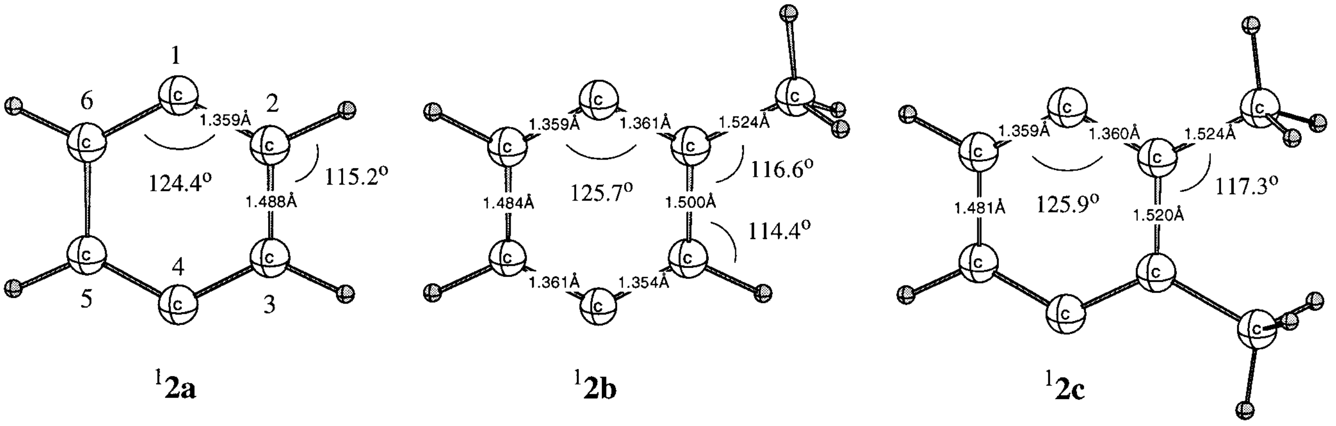

triplets:

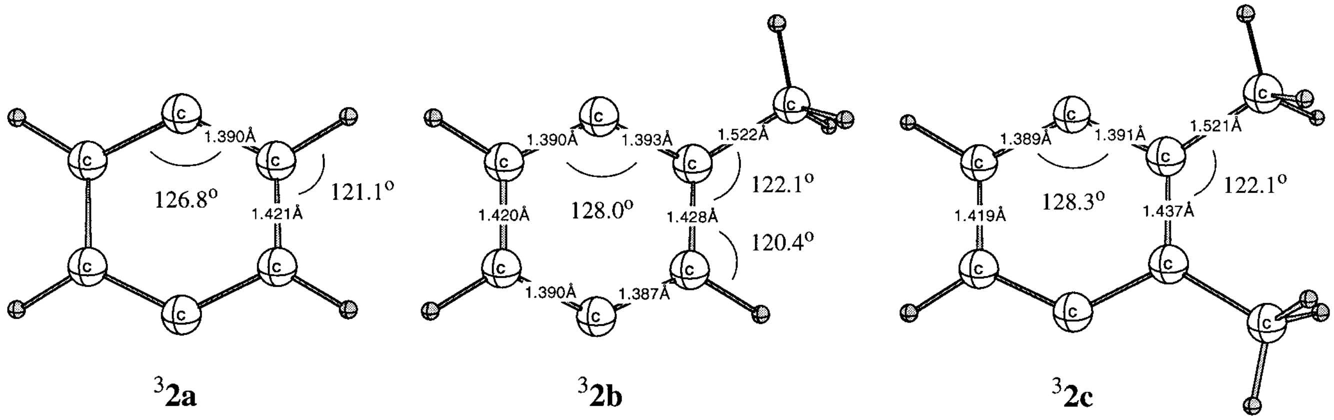

Figure 2. Effect of methyl substitution on *p*-benzyne geometries at BLYP/6-31G*. The larger C2−C3−CH$_3$ angle in ^{1}2c results in a destabilization of the singlet relative to the triplet state by about 3 kcal mol^{-1}. Note also that the C2−C3 bond stretches more in the singlet than the triplet in going from the unsubstituted to the substituted compounds.

1a and **1b** ($\Delta\Delta H_{\mathrm{R,0K}}$ = 12.3 kcal mol^{-1}, Table 4). Hence, dialkyl substitution increases both the activation energy and the reaction endothermicity of the Bergman reaction for *acyclic* enediynes.

Not unexpectedly, both **4a** and **4b** do not cyclize (all optimization attempts only converged to **4a** and **4b**), despite small *d*'s of 2.512 and 2.636 Å, respectively. This is in agreement with Roth and Hopf's finding that aryl-1,2-diyne (**9**, Scheme 1) does not cyclize in the gas phase even at high temperatures (stable up to 280 °C).[42,43] The cyclization products would contain highly strained (olefin strain (OS) = 54.4 kcal mol^{-1}, Table 4)[44] cyclopropene (in **4a**) and cyclobutene moieties (in **4b** and **8**; OS = 30.6 kcal mol^{-1}, Table 4).[44] The strain cannot be compensated by aromatic stabilization (about 21 kcal mol^{-1}).[45]

The hitherto unknown nine-membered ring **4c** was suggested to cyclize spontaneously at room temperature,[8,13] and the computed relatively low activation barrier of 16.3 kcal mol^{-1} (Table 4) for TS4c supports this finding. Note that the MM2 force field gives *d* = 2.84 Å, somewhat too short (2.92 Å at BLYP/6-31G*).[14,21,22]

While **4d** with *d* = 3.413[18,20] cyclizes spontaneously at room temperature, **4e** does not, despite *d* being only slightly larger (3.588 Å).[8,13] In fact, the corresponding activation enthalpies differ by about 7 kcal mol^{-1}! Part of this quantity can be derived from the OS energy difference[44] between the cyclohexene (OS = 2.5 kcal mol^{-1}) and cycloheptene (OS = 6.7 kcal mol^{-1}) moieties in the products.

From the above analysis it is clear that there is no clear-cut relationship between the alkyne carbon distance and the activation energy for Bergman-cyclization of monocyclic enediynes. Nicolaou's "*critical range of 3.31−3.20 Å*",[8,13] however, may still be applicable if severe structural perturbations—such as intramolecular Michael addition in **7**—lead to a structure where *d* falls into this range. Based on the analysis of the present work, the "range" may be extended to 3.4−2.9 Å.

The evaluation of the reaction enthalpy of the Bergman reaction is more problematic than evaluating the heat of formation of **2a** because of the lack of bond-type conservation; i.e., the reaction is not isodesmic and systematic errors do not cancel. The next part of the discussion will therefore only be qualitative. The error in the computed reaction enthalpy of the parent reaction ($\Delta H_{\mathrm{R,0K}}$) is rather large (9.1 kcal mol^{-1}) but is also likely to be systematic, based on the experimental observation that the cyclizations of 9- and 10-membered ring enediynes are reversible and only mildly endothermic.[8,46]

As a consequence of the cyclization endothermicity, the corresponding transition structures for cycloaromatization should be product-like,[19,24] and stereoelectronic effects operative in the

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Table 4. Parameter d (in Å), Activation Enthalpy ($\Delta H^{\ddagger}$, kcal mol^{-1}), Reaction Enthalpy ($\Delta H_{\mathrm{R,0K}}$, kcal mol^{-1}) for the Bergman Reaction of **4a**−**f**, and Reaction Enthalpy for the Formation of the Products via Double Hydrogen Abstraction from 1,4-Cyclohexadiene (Eq 4, $\Delta H_{\mathrm{P,0K}}$); Olefin Ring Strain (OS) of Nonbenzenoid Product Ring and Stability of Enediyne at Room Temperature. Level of Theory: BLYP/6-311+G**//BLYP/6-31G*, Unless Noted Otherwise

$$p\text{-benzyne derivative} + \text{1,4-cyclohexadiene} \rightarrow \text{benzene derivative} + \text{benzene} \tag{4}$$

ring size	species (PG)[e]	d	$\Delta H^{\ddagger}$	$\Delta H_{\mathrm{R,0K}}$	OS[44]	stable at 25 °C	$\Delta H_{\mathrm{P,0K}}$ (eq 4)
	1a (C_{2v})	4.548	28.4	17.6		yes[46]	−122.3[g]
	1b (C_{2v})	4.571	35.6	29.9		yes[46]	−101.3
7	**4a** (C_{2v})	2.512	n.a.[d]	n.a.	54.4	n.a.	n.a.
8	**4b** (C_{2v})	2.636	n.a.[d]	n.a.	30.6	yes[42]	n.a.
9	**4c** (C_s)	2.924	16.3	11.4	6.8	no[13]	−114.5
10	**4d** (C_2)	3.413[a]	25.0[b]	18.3	2.5	no[13]	−111.8
11	**4e** (C_2)	3.588[c]	31.9	25.4	6.7	yes[13]	−106.0
12	**4f** (C_2)[f]	4.353	40.3	36.3	7.4	yes[13]	−97.3

[a] Experimentally estimated distance ca. 3.4 Å.[18,20] [b] Experimental activation barrier = 23.8[13] and 24.0 kcal mol^{-1}.[18,20] [c] Experimental distance (X-ray) = 3.661(5) Å.[13] [d] No ring closure; see text. [e] PG = point group. [f] Using a 6-311G** basis set for the energy single point. Despite extensive efforts, the wave function did not converge with added diffuse ("+") functions on carbon. [g] ZPVE-corrected.

product ground states should in part also be evident in the transition structures.[47] This conclusion is confirmed by the increase in the activation enthalpy (Table 4) of the parent (**1a** → TS1a; $\Delta H^{\ddagger} = 28.4$ kcal mol^{-1}) vs the dimethyl enediyne system (**1b** → TS1b; $\Delta H^{\ddagger} = 35.6$ kcal mol^{-1}). As analyzed above, TS1b already experiences part of the higher relative energy of the product **2c**, where the methyl groups at the olefinic carbons are less stabilizing (eq 3).

It was already noted that **4a** and **4b** do not cyclize, and this can be related to the very large olefin strain energies[44] for the cyclopropene (OS = 54.4 kcal mol^{-1}) and cyclobutene (OS = 30.6 kcal mol^{-1}) moieties in the hypothetical products. Cyclization of **4c** ($\Delta H^{\ddagger} = 16.3$ kcal mol^{-1}) occurs spontaneously at room temperature,[13] where the OS is reduced to 6.8 kcal mol^{-1} (Table 4); the endothermicity is low ($\Delta H_{\mathrm{R,0K}} = 11.4$ kcal mol^{-1}), indicative of a reversible process (the $\Delta H^{\ddagger}$ for the reverse reaction is only 4.9 kcal mol^{-1}).

Final Product Formation. The biradicals **2** and **5** formed after Bergman-cyclization are short-lived and readily abstract hydrogens to reach a closed-shell electron configuration.[17,53b] For a purely qualitative evaluation of the double hydrogen abstraction enthalpy, we evaluated the reaction (eq 4, Table 4, last column) of the p-benzynes **2** and **5** with 1,4-cyclohexadiene, a commonly employed hydrogen donor in experimental studies. The experimental reaction enthalpy ($\Delta H_{\mathrm{P,0K}}$) for **2a** can be estimated from the CH bond enthalpies and the resonance energies as follows:

2CH (**2a** → **3a**)

$$2(-113.5 \pm 0.5)\ \mathrm{kcal\ mol^{-1}}\ ^{40} = -227.0 \pm 1.0\ \mathrm{kcal\ mol^{-1}} \tag{5}$$

2CH (1,4-cyclohexadiene → benzene)

$$2(+73.0 \pm 2)\ \mathrm{kcal\ mol^{-1}}\ ^{49} = +146.0 \pm 4\ \mathrm{kcal\ mol^{-1}} \tag{6}$$

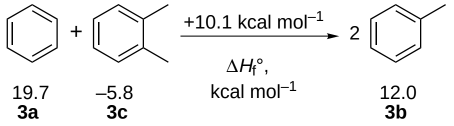
resonance + conjugation energy for benzene formed from 1,4-cyclohexadiene

$$-35.2\ \mathrm{kcal\ mol^{-1}}\ ^{45} \tag{7}$$

$$\text{sum} = \Delta H_{\mathrm{P}}^{\circ} = -116.2 \pm 5\ \mathrm{kcal\ mol^{-1}}$$

This value compares favorably with the computed $\Delta H_{\mathrm{P,0K}} = -122.3$ kcal mol^{-1}; the error bar for this value should include the error in the heat of formation (see above) for **2a**, which is about 7 kcal mol^{-1}.

Intriguingly, there is a continuous decrease in $\Delta H_{\mathrm{P,0K}}$ with increasing alkyl substitution and ring size. The first effect can easily be understood by evaluating[49] isodesmic equation (8),



(8)

which shows an experimental methyl stabilizing effect on benzene of about 10 kcal mol^{-1}. This accounts for most of the 21 kcal mol^{-1} difference in $\Delta H_{\mathrm{P,0K}}$ for **2a** vs **2c** (derived from **1a** and **1b**; see Scheme 1 and Table 4).

However, this effect should be constant for larger alkyl groups and thus does not explain the decrease for larger rings, which implies that either the biradical species becomes more stabilized or that the products are destabilized for larger rings. The first explanation cannot be correct since the $\Delta H_{\mathrm{R,0K}}$'s increase (Table 4). Hence, the closed-shell products must be destabilized. There is a direct correlation between the nonbonded H···H distances and $\Delta H_{\mathrm{P,0K}}$: C1H···HC7 (**6c**) = 2.896 Å; C1H···HC8 (**6d**) = 2.519 Å; C1H···HC9 (**6e**) = 2.265 Å; C1H···HC10 (**6f**) = 2.172 Å (see Supporting Information for Cartesian coordinates of all species), changing from weakly attractive (**6c**) to repulsive (**6f**). Despite this destabilization of the products with larger rings, the exothermicities of eq 5 are still very large. However, this may not always be the case for DNA cleavages where nonstabilized radical centers are generated[8] so that even small energy differences can have a large effect.

Conclusions

Enediyne cyclization chemistry can qualitatively and, for a large part, also quantitatively be studied with pure density functional theory approaches such as BLYP in conjunction with double-ζ (6-31G*, geometries) and triple-ζ (6-311+G**, relative energies) basis sets. The errors are somewhat larger (ca. 3−7 kcal mol^{-1}) than for the much more time-consuming CASPT2 and CCSD(T) (both in error by ca. 2 kcal mol^{-1}) methods with high-quality basis sets. The hybrid functional B3LYP, which normally performs exceptionally well and slightly better than BLYP, displays much larger errors (up to 19 kcal mol^{-1}) due to Hartree−Fock mixing.

The singlet−triplet energy separations (ΔE_{ST}) for p-benzynes are underestimated systematically by about 2 kcal mol^{-1}; this value can be used for a systematic correction. Thus, while

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2-methyl-*p*-benzyne has a ΔE_{ST} (-3.1 kcal mol^{-1}, i.e., singlet ground state) close to that of *p*-benzyne (-3.8 kcal mol^{-1}), 2,3-dimethyl-*p*-benzyne has a ΔE_{ST} of only -0.6 kcal mol^{-1} due to singlet destabilization (methyl repulsion). 2,3-Dialkyl-*p*-benzynes thus have nearly degenerate singlet and triplet states.

The activation enthalpies for the cycloaromatizations are very well reproduced with BLYP. While we find that there is clearly no predictive linear relationship between *d* and $\Delta H^{\ddagger}$, Nicolaou's "*critical range*" for 3.31−3.2 Å, where spontaneous cyclization should occur at room temperature, should be extended to 3.4−2.9 Å. If structural perturbations were to reduce *d* to this distance, cyclization should take place, unless olefin strain is very large.[54]

As a comparison between *p*-benzyne and 2,3-dimethyl-*p*-benzyne shows, alkyl substitution has a large effect on the endothermicity of the Bergman reaction (about 12 kcal mol^{-1}). Since acetylenic bonds are more stabilized by alkyl substitution than olefinic bonds, the reaction endothermicity increases for enediynes which are alkyl substituted at the terminal alkyne carbons. Ring strain effects in monocyclic enediynes, however, can overcome this difference. Thus, the cyclization of a nine-membered enediyne is mildly endothermic; larger rings give larger endothermicities.

The formation of final products via double hydrogen abstraction from 1,4-cyclohexadiene is highly exothermic. The exothermicity decreases with increasing ring size due to unfavorable H•••H repulsion in the products.

Acknowledgment. This work was supported by the Fonds der Chemischen Industrie (Liebig Fellowship) and the Deutsche Forschungsgemeinschaft (Grant Schr 597/1-1). Allocation of computer time by the Regionales Rechenzentrum Niedersachsen (RRZN, Hannover) and the Gesellschaft für wissenschaftliche Datenverarbeitung mbH (GWDG, Göttingen) are gratefully acknowledged. I thank Prof. R. Brückner and Prof. R. R. Squires for valuable comments and Prof. A. de Meijere for his support. Reprints of related papers by Prof. C. J. Cramer and Prof. R. R. Squires were greatly appreciated.

Supporting Information Available: Tables containing Cartesian coordinates of all species (4 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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