Electronic Control of the Bergman Cyclization: The Remarkable Role of Vinyl Substitution

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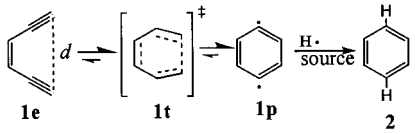
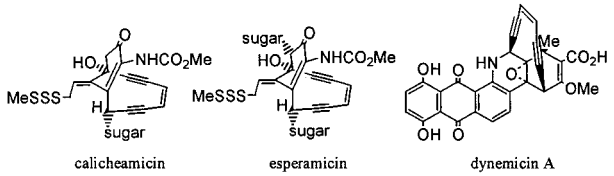
Abstract: We report an ab initio study of the effect of vinyl substitution on the cycloaromatization of 3-ene-1,5-diynes (the Bergman cyclization). The majority of the calculations were conducted by using the BLYP version of Density Functional Theory, and higher level Brueckner orbital calculations were used for a few key compounds. In all, 46 enediynes, 44 cyclization transition states, 39 singlet *p*-benzynes, and 28 related triplet *p*-benzynes were studied, including simple vinyl-substituted and annulated examples. The data indicate that strongly electron-withdrawing groups increase the cyclization barrier, while σ-donating groups decrease it; π conjugation, especially donation, has little effect. Most annulations, including those involving heteroaromatic rings, lower the barrier slightly (6 MR) or raise it slightly (5 MR). Larger effects are seen for smaller rings or charged rings. Some previously observed apparent rate inhibitions are seen to be due to reversibility or forward reactivity of the intermediate *p*-benzynes, which are thereby inhibited from the H abstraction step that completes cycloaromatization. H abstraction reactivity, as judged from the *p*-benzyne singlet−triplet energy gap and from isodesmic equations, is also examined. Unexpected behavior is predicted for some heteroaromatic systems. Finally, we anticipate how these results may be applied to the design of prodrug candidates for subsequent biological application.

Introduction

The Cope rearrangement[1] of hex-3-ene-1,5-diyne (**1e**), which results in concerted cyclization via transition state **1t** to *p*-benzyne (**1p**),[2] was first reported by Bergman[3] in 1972, and has become known as the Bergman cyclization.[4] Included in Bergman's report were instances of intra- and intermolecular trapping of *p*-benzynes to give "cycloaromatized" products (e.g., **2**). In the mid to late 1980s, it became clear that an emerging



series of naturally occurring antibiotics, including calicheamicin, esperamicin, and dynemicin,[5] all operated via Bergman cyclization to a *p*-benzyne derivative, followed by H atom abstraction, especially from DNA.[6] As a consequence of the antibiotics



becoming cycloaromatized, the cell under chemical attack suffered DNA cleavage, ultimately leading to cell death. These biological observations led to the synthesis of many nonnatural targets[7] containing the enediyne "warhead" of the antibiotics, as well as related approaches toward the same goal.[8] All the natural antibiotics, as well as the synthetic mimics, possess an enediyne unit within a medium ring of 9−10 atoms, thus incorporating the strain necessary to enable the cyclization to occur at biologically relevant temperatures. Most of these systems are polycyclic, and contain other adjustable strain-inducing elements,[9] as well as triggering devices which can release a more reactive form of the enediyne upon activation. The utility of this strategy lies in retaining the enediyne in prodrug form until it reaches its biological target, following which the active drug is unveiled. Although several of the naturally occurring enediynes are undergoing clinical evaluation,

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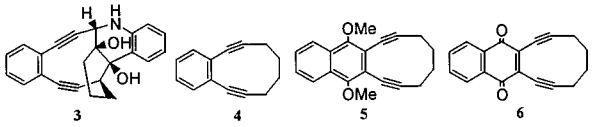
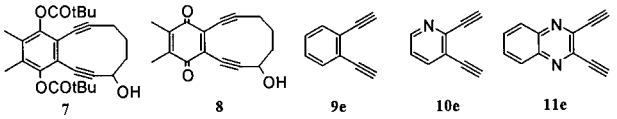
efforts to produce comparable designed enediynes remain a formidable challenge.[10]



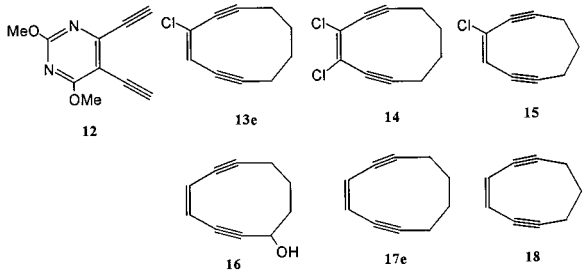
3 4 5 6

On the basis of his extensive studies, Nicolaou[11] proposed that the distance between the terminal acetylenic carbons of the enediyne group (*d*) is a major determinant of reactivity, and values of *d* between 3.20 and 3.31 Å would be necessary for biologically relevant reactivity; recent calculations[12] appear to have extended this range to 2.9−3.4 Å. An effective method to temporarily shorten this distance, thereby raising the ground-state energy for cyclization,[13] has been by the use of transition metal complexation.[14] Certainly differential strain effects between ground and transition states are important.[9,15] Although the least well studied, electronic perturbations can have profound consequences. For example,[16] benzannulation at the ene position of a dynemicin analogue (**3**) or cyclodecenediyne (**4**) resulted in a marked increase in the cyclization barrier. A particularly large cycloaromatization rate difference between hydroquinone derivative **5** (slow) and quinone **6** (fast) prompted the authors to explain the reactivity based on the "extent of double bond character in the ene part of the ene-diyne..."[17] However, the fact that **7** and **8** show almost identical reactivity[18] casts doubt on this explanation; as we discuss later, attention should probably be focused on the effect of the additional aromatic ring in **5** relative to **7**; this point applies to other candidates,



7 8 9e 10e 11e

too (vide infra). Confusion exists regarding the effect of simple benzannulation, since *o*-diethynylbenzene (**9e**) was reported to cyclize more rapidly (E_a = 25.1,[19] 26.2[20] kcal/mol) than **1e** (E_a = 28.2 kcal/mol[21]). Rather than implying that effects on medium ring enediynes differ from those on acyclic enediynes, the apparently discrepant benzannulation cyclization results may be due to changes in the barriers for retrocyclization of the annulated *p*-benzynes vs those for H atom abstraction.[22] At least for the simple cases, it appears that the latter barrier increases slightly (by 0.6 kcal/mol for **9p**), while the former decreases appreciably (by ca. 12 kcal/mol for **9p**). The net effect on kinetic measurements is that the apparent rate of enediyne disappearance is dependent on the concentration of H atom donor, which may vary from one investigation to another. Recognition of this problem has led most investigators to use very large concentrations of H atom donor and/or very reactive H atom donors. Some intriguing effects have been observed with enediynes annulated with heteroaromatic rings.[23] Pyridine **10e** was more reactive (E_a = 21.5 kcal/mol) while quinoxaline **11e** was less reactive (E_a = 33.6 kcal/mol) than **9e**, and pyrimidine **12** was especially reactive (E_a = 16.1 kcal/mol). Clearly there must be several factors operative in these cases to account for the huge range of reactivities reported. Another brief study showed that solvent polarity affects the cyclization rate of **11e**, a result attributed to differential polarity in the enediyne vs its cognizant transition state.[24] Substitution of an anisyl group on the ene position was shown to retard cycloaromatization.[25] Recently, we demonstrated that halo-enediynes, including **13**−**15**, each cyclized more slowly than its unsubstituted parent.[26] Electronic influence may



12 13e 14 15 16 17e 18

also be important for alkynyl substitution. Indeed, alkynyl substitution is known to stabilize the enediyne with respect to cyclization,[27] and accounts for the stability of the strained medium ring enediynes, including the naturally occurring ones. Placement of an OH or OR group on the carbon proximate to the terminal acetylene carbon (as in **16**) has an accelerative effect.[28] Although yet not well understood, we speculate that this is due to an electron-withdrawing decrease in the stabilization afforded alkynes by alkyl substitution; in other words, this may be a ground-state destabilization effect. On the other hand, from work with para-substituted phenyl groups attached to the alkyne unit,[29] others have concluded that the observed electron-withdrawing group (EWG) acceleration is a transition state effect, consistent with theoretical predictions of diminished in-plane π repulsions in the presence of EWG's.[30]

Theoretical treatment of the Bergman cyclization has been inhibited by the high level of theory needed to adequately treat this reaction, and the size of the substituted systems. Cramer,[31] in his recent theoretical paper treating the parent and the 3-aza-enediyne cases,[32] provided an excellent summary of the previous work, as well as the results for a variety of theoretical levels, from density functional theory (DFT) through coupled cluster and multi-configurational methods. Equally important was Schreiner's demonstration that the BLYP version of DFT could be used to adequately describe the key enediyne to transition state segment of the Bergman cyclization reaction coordinate

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for some substituted and medium ring enediynes (e.g., **17e** and **18**, the hydrocarbon parents of **13**−**15**).[12] Very recently, Grafenstein et al.[33] have proposed use of the B3LYP[34] hybrid functional. They argue that BLYP underestimates barriers and was recommended over B3LYP because of its performance in carbene calculations. While B3LYP tends to overestimate barriers and underestimate radical energies, its performance improves with basis set size, and corrections may be made by using a "sum" formula (apparently performed only for **1**). Others have recently warned that B3LYP may produce spurious diradical intermediates in Cope rearrangements.[35]

Computational Methods

Molecular geometries for all species were initially optimized by using the BLYP (Becke−Lee−Yang−Parr) functional,[36,37] as implemented in the Gaussian 98 program package[38] installed on a Pentium PC; all optimizations employed the 6-31G* basis set. As expected from previous work on the parent system, all enediynes and transition states leading to *p*-benzynes had restricted wave functions that were stable. All *p*-benzynes, however, had restricted wave functions which were unstable with respect to becoming unrestricted. Therefore, "broken-symmetry" singlet wave function (BS-UDFT) energies at the restricted geometries were calculated for each case. These energies were always lower than the restricted energies, and the total spin expectation values for Slater determinants formed from the unrestricted Kohn−Sham orbitals were between 0.5 and 1.0. Many (26) of the *p*-benzynes were then re-optimized by using unrestricted DFT (UBLYP), which resulted in lowered energies of anywhere between about 2 and 6 kcal/mol, but every case could not be reoptimized due to time restrictions. In two of the annulated cases, attempted *p*-benzyne optimization using restricted wave functions failed due to ring opening; each time unrestricted theory successfully provided a *p*-benzyne minimum. In all, 31 of the 39 *p*-benzynes reported herein were optimized at the BS-UDFT level. Every stationary point was subjected to analytical vibrational frequency analysis to confirm its optimized stationary point nature, and to calculate the zero-point vibrational energies (ZPVE) and thermal enthalpy contributions ($H_{298} - H_0$). All enediynes and *p*-benzynes were confirmed as local minima (NIMAG=0) and all transition states as first-order saddle points (NIMAG=1), unless specified otherwise. The energies reported include the unscaled vibrational and thermal enthalpy corrections at the 6-31G* level (although the electronic energies may have been calculated by using a larger basis set), except for the singlet−triplet energy gaps, which include only the vibrational energy corrections. A single point energy for every structure was also obtained by using the 6-311+G** basis set. In addition, the cc-pVDZ and cc-pVTZ basis sets[39] were used for a limited set of structures for comparison purposes.

Single point energies for select structures were also obtained by using Brueckner orbitals[40] with perturbative estimations of the effect of triple excitations [BCCD(T)] using the 6-31G* basis set. They were carried out using a restricted HF reference wave function [RBCCD(T)] rather than an unrestricted one [UBCCD(T)] because the latter calculation did not converge at the initiation point. These calculations take on the order of 100 times as long as the corresponding BLYP/6-31G* ones, which precluded the use of the 6-311+G** basis set.

Electronic energies and vibrational corrections were also obtained for the related molecules necessary to complete the isodesmic equations discussed below.

Although not beyond criticism,[41] a simple method for DFT spin correction of unrestricted singlets has been developed, and was applied to most of the *p*-benzynes in this study.[42] To do so simply requires calculation of the energy of the vertical triplet species, as well as the spin expectation values mentioned above (which were 2.0 for all triplets). Because we found that the spin corrections for **1** (BLYP and B3LYP) and **19**−**22** (B3LYP) were nearly the same with either the 6-31G* or 6-311+G** basis sets, we adopted the smaller basis set for all other corrections. For two cases (X = sulfoxyl and phenyl, Table 2), the spin corrections are to UDFT energy values for *R*-optimized geometries.

We feel it is worth commenting on a technical problem encountered for several cases when computing the broken-symmetry energies. Despite destroying the $\alpha-\beta$ and spatial symmetries by mixing the HOMO and LUMO, these geometries gave converged *restricted* wave functions using the default SCF procedure. However, using a (very time-consuming) quadratically convergent SCF procedure,[43] most, but not all, cases led to converged unrestricted wave functions. In no case did we fail to obtain an unrestricted wave function result for both the 6-31G* and 6-311+G** basis sets. We emphasize that this reversion to a restricted wave function result occurred unpredictably: sometimes with the smaller, sometimes with the larger basis set, and sometimes during an attempted UBLYP/6-31G* optimization. UBLYP optimizations usually ran best when a new guess wave function was generated at each optimization step [achieved via the guess = (mix, always) command], rather than the default technique of using the wave function from the previous step as the starting point for the new step.

Results and Discussion

Choice of Theoretical Approach. It was previously shown[12] that the BLYP method gives reasonably accurate results for the cyclization enthalpy of activation for the parent (**1e**) case (24.3 kcal/mol at 6-31G*, 27.4 kcal/mol at 6-311+G**, 27.5 kcal/mol at cc-pVTZ[44] vs an experimental value of 28.7 kcal/mol). The BPW91 DFT method used by Cramer produces consistently lower values for the cyclization activation enthalpies (22.1 kcal/mol at 6-31G*,[8] 22.0 kcal/mol at cc-pVDZ) and more so for the relative *p*-benzyne enthalpy (R geometry: BPW91, 7.2 kcal/mol at 6-31G*, 7.0 kcal/mol at cc-pVDZ; BLYP, 12.1 kcal/mol at 6-31G*, 18.0 kcal/mol at 6-311+G**, 18.3 kcal/mol at cc-pVTZ; U geometry: BPW91, 0.9 kcal/mol at cc-pVDZ; BLYP, 7.3 kcal/mol at 6-31G*, 14.3 kcal/mol at 6-311+G**); the experimental value is about 8.5 kcal/mol.[20,45] It is seen that, as discussed previously, this level of theory does not adequately treat the *p*-benzyne diradical; the lesser basis sets give fortuitously close to correct values, but the better basis sets show considerable divergence from reality. Importantly, it seems that the 6-311+G** results are virtually the same as the cc-pVTZ

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values at considerably lesser cost. The possibility that the more popular B3LYP method would perform better with the larger basis set, as was shown for **1**,[33] led us to also use this functional for our key halogen-substituted compounds (see Table 1); the calculated trends were the same. So that we could compare some of our results to those previously obtained with BLYP, we have chosen to use primarily that version of DFT. To validate some of our conclusions, we have also employed the BCCD(T) method, which was shown to be better than the CCSD(T) approach for this problem.

Geometries. Cartesian coordinates and energies for all optimized stationary points are given in the Supporting Information section. Figure 3 shows ball-and-stick diagrams of selected structures, including heavy atom bond distances. Optimization of all the arenes, radicals, triplet benzynes, enediynes, and transition state structures for the Bergman cyclization was relatively straightforward. The distances between the terminal acetylenic enediyne carbons ($r(C_1C_6) = d$) were fairly constant in the range of 4.3 to 4.6 Å for the 25 acyclic enediynes studied, as were the values for d (2.03 to 2.12 Å) in the 25 associated transition states (cf Table 2). It should be noted that many of the enediynes have slightly bent acetylene units, with bond angles in the 175−180° range (enforced 180° bond angles were often less stable by at least 0.1 kcal/mol). This has been observed previously, and attributed to in-plane $\pi-\pi$ repulsion between the acetylene units.[46] Accordingly, enediynes that have larger d values should be less distorted from linearity. The trio of **48** ($d = 4.337$ Å), **23** ($d = 4.626$ Å), and **54** ($d = 5.130$ Å) illustrate this effect clearly: CCC = 175.5°, 177.1°, 178.1° and CCH = 177.5°, 178.3°, 179.1°, respectively. However, other factors can come into play, as in **9** ($d = 4.254$ Å), where the triple bonds are closer than in any of the previous three, and CCC = 178.1°and CCH = 178.7°. Although there is an aromatic ring, it cannot conjugate with the in-plane π bonds, so the effect on linearity is not straightforward. All enediynes and transition states have their central 6 carbons and 4 attached atoms in the same plane.

Optimization of the singlet *p*-benzynes was more complicated. Many of the substituted cases gave restricted (R) geometries in which the benzyne ring was nonplanar. Some produced planar structures that had one imaginary frequency, which led to distortion to a nonplanar minimum. The energy difference between planar and nonplanar benzynes ranged from 0.1 (2-fluoro-) to 1.7 kcal/mol (2,3-difluoro-). However, in every case, the planar structure gave a lower energy when unrestricted (U) wave functions were used. And reoptimization of the R geometries using U wave functions always produced lower energy planar structures, which were minima. To get a higher level theoretical sense of whether the nonplanar structures might really be lower in energy, we obtained single point BCCD(T)/6-31G* relative energies for the various 2-fluoro-*p*-benzyne optimized structures: R-optimized nonplanar (5.5 kcal/mol), R-optimized planar (4.7 kcal/mol), and U-optimized planar (0.0 kcal/mol).[47] We thus conclude that, at least for the examples reported herein, the *p*-benzynes are all planar. However, since we were not able to U-optimize all the *p*-benzynes, some are R-optimized nonplanar ones, and thus have higher energies than they should. Since the emphasis (at least for the 8 R-optimized *p*-benzynes) is on the relative energies of the enediynes and their associated transition states, and since the relative enthalpies of the *p*-benzynes are not accurate anyway at the density functional level of theory, the improper *p*-benzyne structures can be tolerated.

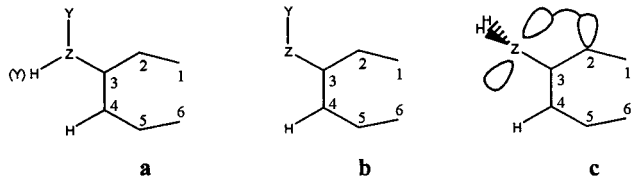


Figure 1. Most prevalent substituent orientations.

The geometries of most of the polyatomic substituents are as shown in Figure 1a [larger atom, if unsymmetrical, on Z pointed away from the neighboring H_4 and toward the lone pair or (developing) radical center at C_2: examples include −CHO, −NHCHO, $-NO_2$, −planarized NH_2, and $-BH_2$] or Figure 1b (lone atom on Z pointed toward C_2: examples are −OH and −OCHO). For amino and borano groups, structures constrained as in Figure 1c were investigated; these and related structures are discussed separately. For the sulfoxyl substituent [−S(O)H], the enediyne and transition state structures have the sulfur lone pair pointed toward C_2, and approximately coplanar with the 6 carbon atoms. Despite the stationary point nature of these sulfoxyl structures, there may be lower energy rotamers, but the cyclization activation enthalpy is probably as correct as any of the others.

Test Case: Can Theory Explain the Impact of Chlorine Substitution on Cyclization? An impetus for this work was the experimental observation that 3-chlorocyclonon-3-ene-1,5-diyne (**15**), 3-chlorocyclodec-3-ene-1,5-diyne (**13e**), and 3,4-dichlorocyclodec-3-ene-1,5-diyne (**14**) cycloaromatize more slowly than their unsubstituted counterparts. Why is this so? There are three possible factors that could be responsible: (1) the cyclization barriers are *higher* for the Cl-substituted cases; (2) the *p*-benzyne ring-opening barriers are *lower* for the Cl-substituted cases (as was found for the 3-azahex-3-ene-1,5-diyne case[26,27]); and (3) the Cl-substituted *p*-benzynes are relatively more stable to H atom abstraction, which extends their half-lives, thus increasing the likelihood of cycloreversion.

As elucidated by Logan and Chen,[48] the singlet−triplet energy gap is a measure of the reactivity of diradicals relative to radicals, with "noninteracting" triplets having approximately radical reactivity, and the lower energy singlets showing proportionally lower reactivity.[49,50] The experimental value for the $\Delta E(_{ST})$ for **1p** is 3.8 kcal/mol.[51] As shown in Table 1, the $\Delta E(_{ST})$ clearly decreases as halogens are added to the *p*-benzyne structure, thereby signaling an increase in H atom abstraction rate with halogenation.[52] This, of course, is opposite to the observed reactivity decrease, thereby eliminating explanation (3) above (vide infra for further discussion of H atom abstractions). Table 1 also shows the room-temperature calculated

(46) Kraka, E.; Cremer, D. *J. Mol. Struct., THEOCHEM* **2000**, *506*, 191.

(47) The U-opted planar 2,3-difluoro-*p*-benzyne was 6.7 kcal/mol lower in energy than its R-opted planar counterpart at the BCCD(T)/6-31G* level.

(48) Logan, C. F.; Chen, P. *J. Am. Chem. Soc.* **1996**, *118*, 2113.

(49) Kraka, E.; Cremer, D.; Bucher, G.; Wandel, H.; Sander, W. *Chem. Phys. Lett.* **1997**, *268*, 313.

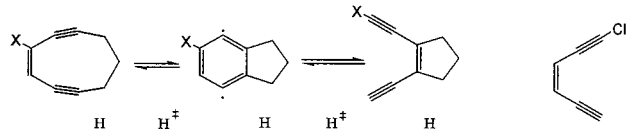
(50) In a recent paper (Okuno, Y.; Iwashita, T.; Sugiura, Y. *J. Am. Chem. Soc.* **2000**, *122*, 6848), the authors calculate a 0.04 kcal/mol change in $\Delta E(_{ST})$ for the *p*-benzyne from the antitumor antibiotic C-1027 upon going from the nonreactive to reactive environment. They suggest that the drug's change in reactivity is, therefore, related to a change in H atom abstraction rates. However, such a small energy change cannot account for the drug's switch from stability to reactivity, which corresponds to a reactivity change of at least 1−2 kcal/mol. The explanation for C-1027's stability more likely lies in its sequestration via its apoprotein.

(51) Wenthold, P. G.; Squires, R. R.; Lineberger, W. C. *J. Am. Chem. Soc.* **1998**, *120*, 5279.

(52) Our $\Delta E(_{ST})$ for **1p** is larger than that given by Schreiner[11] because we use the U-optimized reference structure for singlet **1p**, while he uses the R-optimized one.

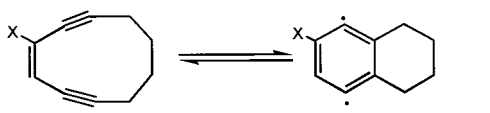
enthalpies (H_{298}) for the parent (**1**), monofluoro- (**19**), difluoro- (**20**), chloro- (**21**), and dichloro- (**22**) cases. It is clear that both DFT (BLYP and B3LYP—where the latter appears to perform better with respect to the *p*-benzyne energies with the better basis set) and BD levels of theory indicate that the cyclization barrier increases as the vinylic hydrogens are replaced with fluorine or chlorine atoms, with the latter exhibiting a slightly diminished effect relative to the former (the reasons for this will be discussed later). At the BD level, the effect is about 5 kcal/mol for the first F and about 3 kcal/mol for the second one. At the same time, it is seen that the cycloreversion barriers stay flat to increasing somewhat less than the cyclization barriers. This combination of effects means that explanation (1), but not (2), can account for the aforementioned experimental observations.

It might have already been inferred from the stability of **15** that explanation (1) was correct, as the intermediate cyclopentano-*p*-benzyne (**15p**) might have been expected to cyclorevert to 1-(2-chloroethynyl)-2-ethynylcyclopentene (**24e**), had it been



a: **18**, X = H (0.0) 15.4 (**23p**) 12.1 22.7 (**23e**) -5.0 kcal/mol
b: **15**, X = Cl (0.0) 16.9 (**15p**) - 27.0 (**24e**) -0.2 kcal/mol

formed. As suggested by the data[53] shown below, both the parent and chloro-substituted cyclopentene diynes are more stable than the corresponding medium ring enediynes. However, the cyclization barriers show quite the opposite trend, in accord with the established idea that alkylation stabilizes triple bonds more than double bonds (and this is felt in the transition state), and this offsets the strain associated with the medium ring. In fact, the vinylic alkylation has essentially no effect on the cyclization barrier relative to H (also seen below for Me substitution). Chlorine, as expected, destabilizes the triple bond relative to the double bond [1-chlorohex-3-ene-1,5-diyne (**25e**) is 4.8 kcal/mol higher in enthalpy than 3-chlorohex-3-ene-1,5-diyne (**21e**) at BLYP/6-311+G**], which makes the cycloreversion of the *p*-benzyne to the medium ring even more favorable. Thus the nonproduction of **24e** is not a decisive observation.



17e, X = H (0.0) 23.7 (**17p**) 14.1 kcal/mol
13e, X = Cl (0.0) 26.0 (**13p**) 15.6 kcal/mol

Finally, we had to consider the possibility that the results for the acyclic cases (halo-substituted vs unsubstituted) might not apply to the cyclic molecules. To this end we calculated the cyclization parameters for **13e** and **17e** themselves. The

Table 1. Relative Enthalpies (H_{298}, kcal/mol) of Stationary Points for Halogen Substituents[a]

compd.	level of theory	enediyne (e)	transition state (t)	p-benzyne[b] (p)		
		H_{rel}	H_{rel}	H_{rel}	$H_{rel}(SC)$[c]	$\Delta E(_{ST})$[d]
X=Y=H (1)	BLYP/6-31G*	0.0	24.3	7.3	3.7	4.6 (8.2)
	BLYP/6-311+G**	0.0	27.4	14.3	10.6	5.1 (8.8)
	B3LYP/6-31G*	0.0	29.8	3.9	0.7	2.7 (5.9)
	B3LYP/6-311+G**	0.0	32.5	10.7	7.4	3.0 (6.3)
	BCCD(T)/6-31G*[e]	0.0	25.6	4.8	-	-
X=F, Y=H (19)	BLYP/6-31G*	0.0	25.4	8.7	6.2	2.6 (5.1)
	BLYP/6-311+G**	0.0	29.1	16.0	13.5	2.7 (5.2)
	B3LYP/6-31G*	0.0	30.8	4.5	2.6	1.5 (3.4)
	B3LYP/6-311+G**	0.0	34.0	11.4	9.5	1.5 (3.4)
	BCCD(T)/6-31G*	0.0	30.5	7.9	-	-
X=Y=F (20)	BLYP/6-31G*	0.0	28.3	9.7	8.9	0.7 (1.5)
	BLYP/6-311+G**	0.0	32.7	17.3	16.5	0.5 (1.3)
	B3LYP/6-31G*	0.0	33.7	4.4	3.9	0.3 (0.8)
	B3LYP/6-311+G**	0.0	37.5	11.5	11.0	0.2 (0.7)
	BCCD(T)/6-31G*	0.0	33.2	7.6	-	-
X=Cl, Y=H (21)	BLYP/6-31G*	0.0	25.5	7.8	5.4	2.5 (4.9)
	BLYP/6-311+G**	0.0	28.9	15.0	12.6	2.7 (5.1)
	B3LYP/6-31G*	0.0	31.0	3.5	1.6	1.5 (3.4)
	B3LYP/6-311+G**	0.0	33.9	10.4	8.4	1.6 (3.6)
X=Y= Cl (22)	BLYP/6-31G*	0.0	27.6	8.0	7.2	0.8 (1.6)
	BLYP/6-311+G**	0.0	31.5	15.4	14.6	0.8 (1.6)
	B3LYP/6-31G*	0.0	33.0	3.0	2.3	0.5 (1.2)
	B3LYP/6-311+G**	0.0	36.4	10.0	9.3	0.5 (1.2)

[a] Geometries and thermal rovibrational contributions from the BLYP/6-31G* level; since actual B3LYP/6-31G* rovibrational corrections for **1** were only 0.1−0.3 kcal/mol different from the BLYP/6-31G* corrections, the latter were used throughout. [b] For the *p*-benzynes, the values are from UBLYP (broken spin symmetry) optimizations and rovibrational corrections. [c] These values are corrected for spin contamination effects according to the method described in ref 42; see text for discussion. [d] $\Delta E(_{ST})$ is the singlet−triplet energy gap, including ZPVE corrections from the BLYP/6-31G* level; parenthetical values include the spin contamination correction; a positive value indicates the triplet lies above the singlet. [e] Values taken from ref 31.

6-311+G** data shown below (the *p*-benzyne enthalpy values are for BS-DFT calculations on restricted geometries) prove that the acyclic and cyclic substituent effects are quite similar, with the barrier enhancing effect of Cl somewhat greater (2.3 kcal/mol) in the medium ring case than in the acyclic enediyne (1.5 kcal/mol). The transition state *d* values (1.973 Å unsubstituted vs 1.945 Å substituted) are consistent with an earlier transition state for the less endothermic, unsubstituted case. It should be noted that the experimental values for the activation barrier for **17e** (23.8[54] and 24.0[55] kcal/mol) are quite close to our calculated value of 23.7 kcal/mol.

Substituent Effects. With the knowledge that halogens raise the cyclization barrier for enediynes, we proceeded to investigate the effects of other substituents, in part to understand the general substituent pattern, and in part to find substituent combinations that might prove useful as prodrug/drug pairs in biological applications. Table 2 is a compilation of the relative energies of the species studied; also included are the *d* values, substituent stabilization enthalpies as calculated from isodesmic eq 1, and spin contamination corrections for most of the *p*-benzynes.

(1) Phenyl Substitution. As mentioned in the Introduction, an anisyl group (**44**) resulted in about a 3 kcal/mol increase in the cyclization free energy barrier relative to the corresponding

(53) The enthalpy values shown were obtained by combining Schreiner's[11] RBLYP/6-311+G** results for cyclonona-3-ene-1,5-diyne (**18**) and cyclopentano-*p*-benzyne with our results at the same level for the latter benzyne and 1,2-diethynylcyclopentene. The chloro-substituted results were generated by adding the difference in the relative cyclization activation barriers for 3-chlorohex-3-ene-1,5-diyne and the parent enediyne to the X = H medium ring cyclization barrier and the difference for 1-chlorohex-3-ene-1,5-diyne and the parent to the X = H cyclopentene barrier.

(54) Nicolaou, K. C.; Zuccarello, G.; Ogawa, Y.; Schweiger, E. J.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 4866.

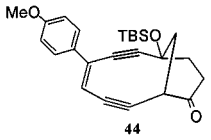
(55) Magnus, P.; Fairhurst, R. A. *J. Chem. Soc., Chem. Commun*. **1994**, 1541.

Table 2. Relative Enthalpies (H_{298}, kcal/mol) of Stationary Points for Various Substituents[a]

compd.	enediyne (e)			transition state (t)		p-benzyne[b] (p)			
	H_{rel}	E_s[n]	d (Å)	H_{rel}	d (Å)	H_{rel} (H_{rel})	H_{rel} (SC)[o]	$\Delta E(_{ST})$[p]	r_{ab}(Å)[q]
X=Y=H (**1**)	0.0	0.0	4.546	27.4	2.078	14.3 (18.0)	10.6	5.1	2.719
X,Y=$(CH_2)_3$ (**23**)	0.0	-	4.626	27.7	2.099	14.7 (17.1)	10.5	6.6	2.739
X=Me, Y=H (**26**)	0.0	4.5	4.434	27.5	2.067	14.7 (18.5)	11.2	4.6	2.710
X=CHO, Y=H (**27**)	0.0	4.6	4.482	27.3	2.071	14.7 (18.2)	11.0	-	-
X=Cl, Y=H (**21**)	0.0	1.9	4.477	28.9	2.046	15.0 (20.8)	12.6	2.7	2.711
X=Y=Cl (**22**)	0.0	-	4.325	31.5	2.006	15.4 (25.2[i])	14.6	0.8	2.685
X=F, Y=H (**19**)	0.0	5.5	4.544	29.1	2.039	16.0 (21.8[i])	13.5	2.7	2.724
X=Y=F (**20**)	0.0	-	4.523	32.7	2.036	17.3 (26.2[i])	16.5	0.5	2.713
X=NO_2, Y=H (**28**)	0.0	0.4	4.458	28.6	2.047	14.7 (20.5)	12.2	2.7	2.724
X=OH, Y=H (**29**)	0.0	10.6	4.394	27.3	2.049	15.1 (19.8[i])	12.4	3.2	2.712
X=OCHO, Y=H (**30**)	0.0	3.4	4.415	25.4	2.065	12.6 (16.6)	9.5	-	-
X=NH_2 (pyr), Y=H (**31**)	0.0	11.8	4.423	27.2	2.056	15.5 (19.6[i])	12.5	3.7	2.709
X=NH_2 (pl, copl), Y=H (**32**)	0.0[c]	-	4.416	27.2[f]	2.054	na (19.6)[j]	-	-	-
X=NH_2 (pl, perp), Y=H (**33**)	0.0[d]	-	4.437	28.6[g]	2.056	na (17.6)[d]	-	-	-
X=NHCHO, Y=H (**34**)	0.0	5.9	4.305	25.7	2.059	13.5 (17.8[i])	10.4	-	-
X=NH_3^+, Y=H (**35**)	0.0	1.8	4.620	28.0	2.034	15.4 (21.1)	12.9	2.7	2.717
X=BH_2 (copl), Y=H (**36**)	0.0	6.8	4.413	25.3	2.096	12.4 (15.3)	8.2	6.2	2.723
X=BH_2 (perp), Y=H (**37**)	0.0[e]	-	4.388	26.2[h]	2.108	12.5[l] (15.1)[e]	-	-	-
X=BH_3^-, Y=H (**38**)	0.0	24.5	4.393	26.9	2.121	13.7 (14.3)	9.8	9.2	2.723
X=SH, Y=H (**39**)	0.0	4.0	4.461	27.7	2.061	14.7 (na)	11.8	3.7	2.707
X=S(O)H, Y=H (**40**)	0.0	-1.3	4.414	27.0	2.092	12.4 (15.9)[m]	8.2[m]	-[m]	-
X=Ph, Y=H (**41**)	0.0	-	4.321	26.8	2.060	14.8[k] (17.9[i])	10.4[k]	-	-
X=*p*F-Ph, Y=H (**42**)	0.0	-	4.321	26.8	2.058	14.9[k] (18.0[i])	-	-	-
X=*p*BH_2-Ph, Y=H (**43**)	0.0	-	4.312	26.7	2.058	14.7[k] (17.8[i])	-	-	-

[a] Geometries and thermal rovibrational contributions from the BLYP/6-31G* level, electronic energies from the BLYP/6-311+G** level; absolute enthalpies (298 K, hartrees) for enediynes: **1e**, −230.78940; **13e**, −846.31139; **17e**, −386.69118; **19e**, −330.06346; **20e**, −429.33128; **21e**, −690.40756; **22e**, −1150.02199; **23e**, −347.42548; **26e**, −270.06270; **27e**, −344.11953; **28e**, −435.34391; **29e**, −306.02601; **30e**, −419.35644; **31e**, −286.13332; **32e**, −286.13360; **33e**, −286.11857; **34e**, −399.47630; **35e**, −286.45510; **36e**, −256.20119; **37e**, −256.19022; **38e**, −256.85203; **39e**, −628.98860; **40e**, −704.16517; **41e**, −461.71715; **42e**, −560.99583; **43e**, −487.12913. [b] For the *p*-benzynes, the nonparenthetical values are from UBLYP (broken spin symmetry) optimizations and rovibrational corrections, while the parenthetical values are from all-restricted computations and all electronic energies are from calculations using the 6-311+G** basis. [c] This structure has NIMAG=1, corresponding to pyramidalizing the NH_2 group. [d] This structure has NIMAG=2, corresponding to rotation and pyramidalization of the NH_2 group. [e] This structure has NIMAG=1, corresponding to rotation of the BH_2 group. [f] This structure has NIMAG=3, with extra imaginary frequencies for pyramidalization and deplanarization. [g] This structure has NIMAG=3, with extra imaginary frequencies for rotation and pyramidalization. [h] This structure has NIMAG=2, where the extra imaginary frequency corresponds to rotation of the BH_2 group. [i] The parenthetical value is for the nonplanar R-optimized minimum. [j] This structure has NIMAG=2, corresponding to two possible modes of coupled NH_2 pyramidalization/ring deplanarization; thus a slightly lower energy structure with a planar/coplanar amino group exists on the R-surface, but is meaningless. [k] UBLYP/6-311+G**//BLYP/6-31G* value, since broken symmetry optimization was not affected in this case; the U-optimized value would be somewhat less. [l] Not quite U-optimized (within 10−8 hartrees) despite many cycles and exact calculation of Hessian; vibrational correction estimated. [m] The nonparenthetical value is estimated from UBLYP/6-31G*//BLYP/6-31G*, as an unrestricted energy at 6-311+G** could not be obtained; the parenthetical value is for the nonplanar R-optimized minimum; the triplet state was optimized, and its geometry is included in Figure 3, but its energy, 1 kcal/mol above the U-value for the R-singlet, is not particularly meaningful. [n] E_s is the relative enthalpic stabilization, in kcal/mol, of the enediyne induced by the substituent, as judged from isodesmic eq 1 at the BLYP/6-311+G**//BLYP/6−31G* level. [o] Spin corrected enthalpies of BSDFT singlet energies—see text for details. [p] This parameter is defined in Table 1. [q] R_{ab} is the distance between the radical centers in the benzynes.

enediyne with the anisyl replaced by H. Since our calculations suggest that relative entropy factors are essentially constant, this must translate primarily into enthalpy effects. The authors suggested that interaction with the phenyl ring would be relatively less important in the transition state, thereby attributing the rate retardation to ground state stabilization; our results (see below) indicate relatively strong conjugative effects in the transition state. As is seen from Table 2, our calculations indicate an approximately 1 kcal/mol *decrease* in the cyclization barrier (**41**−**43** vs **1**), in contrast to the results for **44**. However, subtle conformational effects may be at play here, perhaps including interaction between the OTBS group at the bridgehead of **44** with the electron rich anisyl group which might cause the anisyl to adopt a dihedral angle relationship with the enediyne unit that is not ideal for cyclization assistance (cf. our discussion of the effect of rotating the amino substituent on the cyclization barrier), and thereby lead to the observed retardation.



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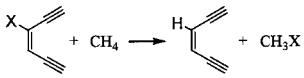
In the cases studied here, it is clear that the electronic effects of F and BH_2, which are significant, and in the opposite direction, when attached directly to the vinylic position of the enediyne unit, are completely damped out when they are relegated to the para position of the phenyl substituent. It should be noted that the structures of the three phenyl-substituted cases are as similar as the energetics. The dihedral angles between the phenyl ring and the vinyl group to which it is attached are 23.3−24.7° for the enediynes, 17.0−20.0° for the transition states, and 26.6−29.4° for the *p*-benzynes, which allow for significant conjugation.



(1)

(2) Directly Attached Substituents.[56] The standard approach to substituent effects is to try to distinguish σ (inductive) from π (resonance) effects, with hyperconjugative and field effect contributions usually relegated to a minor role. The non-π substituents studied, NH_3^+, CH_3, $(CH_2)_3$, and BH_3^-, support the idea that σ-donors decrease the cyclization barrier, while σ withdrawing groups raise the barrier, although the effect is only about 0.5 kcal/mol in each direction. It is interesting that these substituents also raise and lower the relative energy of their respective *p*-benzynes in the same direction as they effect the cyclization barrier. As implied by the stabilization energy derived from isodesmic eq 1, the effect of BH_3^- is enormous, and must be felt even more at the transition state.

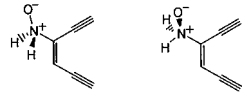
Most of the other substituents have either filled or empty p orbitals, and should, therefore, exhibit conjugative effects. It is immediately apparent that no straightforward linear free energy relationship will emerge. For example, the CHO (formyl) and F substituents are electron withdrawing (but for different reasons, although both have about the same σ_m) and OH is strongly π donating, yet CHO and OH have essentially no effect on the cyclization barrier, while F raises it the most. While the latter is strongly σ withdrawing, OH is too (relative to C or H), but it has no effect. Why? It is clear that π donation weakly lowers the barrier, and this effect often conflicts with σ withdrawal, which has the opposite effect. Thus NH_2 (either the natural pyramidal form,[57] or the enforced planar/coplanar form) has almost no net effect, nor does OH. NO_2 raises the barrier appreciably due, probably, to its very strong electron-withdrawing capacity (note that its E_s indicates it barely stabilizes the enediyne structure relative to methyl). The ester (OCHO) and amide (NHCHO) results appear anomalous (lower barriers), but this may be due to an enediyne ground state, rather than the more usual transition state, effect. In accord with this possibility, we note that the ester and amide *p*-benzynes are relatively low in energy, consistent with a "less stabilized" enediyne. Inspection of the E_s values reveals that the ester and amide each stabilize the enediyne moiety much less than the alcohol and amine. If stabilization of the transition states is somewhat differentially smaller, then the lower barriers would result.

This leaves us to explain the strong effects of halogens. We considered the possibility that direct (through space) interaction of an in-plane orbital with the developing radical center could either destabilize (when the orbital is filled) or stabilize (when the orbital is empty) the transition state (cf. Figure 1c). Such an effect would explain the benign effect of OH (which has a conformation as in Figure 1b) and might also account for the increased retardation predicted for a perpendicular NH_2 group over a coplanar one (cf. Table 2, entries 12−14). The only slightly greater effect of F over Cl can be understood when it is noted that the expectedly strong in-plane effect of F is somewhat offset by its relatively greater stabilizing effect on the enediyne (see E_s values in Table 2). Interestingly, a fixed perpendicular NO_2 group has a slightly *accelerative* effect (0.2 kcal/mol), consistent with the "lone pair" on the N of the nitro group really being delocalized onto the oxygens.[58] To probe this effect further, we calculated the effect of moving the N (B) with respect to the developing radical center by changing the value of α from the optimized value (cf. Figure 2: α was varied by moving the N (B) and keeping all other geometrical parameters constant; the energy values are electronic energies only, i.e., not ZPVE corrected). It is seen that moving the coplanar NH_2 group toward the developing radical center actually decreases the barrier. The data show the ground state to be more destabilized by the smaller α, while the transition state is more destabilized by the larger α. The effects are

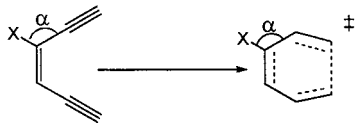
(56) The effect of these substituents on cycloreversion of the *p*-benzynes to the corresponding 1-substituted hexa-3-ene-1,5-diynes was not studied, except for the aforementioned Cl (**25t**, barrier 2.8 kcal/mol higher to a 4.8 kcal/mol less stable 1-chlorohexa-3-ene-1,5-diyne, **25e**) and pyramidal NH_2 (**31t′**, barrier 2.1 kcal/mol higher to a 0.1 kcal/mol more stable 1-aminohexa-3-ene-1,5−diyne, **31e′**). The NH_2 result is significant with respect to the effect of neighboring unsaturated nitrogen in the annulated cases discussed herein.

(57) Both amino enediynes, transition states, and the *p*-benzyne are all pyramidal, with the lone pair "aligning" with the plane of the six carbons. The inversion barriers (BLYP/6-311+G**) are as follows: 3-amino enediyne, 0.5 kcal/mol; corresponding transition state, 1.2 kcal/mol; *p*-benzyne, 1.6 kcal/mol. Aniline, on the other hand, is totally planar. The low inversion barriers are clearly due to conjugation. For a 90° rotated NH_2 structure, the 3-amino enediyne inversion barriers are 1.8 and 5.3 kcal/mol (2 pyramidal forms, with the one with the lone pair facing the vinylic H favored), while the *p*-benzyne barriers are 1.9 and 3.2 kcal/mol (again favoring the form with the lone pair facing the neighboring H); for aniline, the comparable barrier is 3.4 kcal/mol.

(58) There may also be an in-plane retardation from the 1,4-interaction of a filled orbital on the oxygen atom of the NO_2 group with the proximal developing radical center. The evidence for this comes from preliminary results for the amine oxide case. Two conformations were considered (ONCC dihedral angle held fixed), and the cyclization barrier for **i** was calculated to be about 1 kcal/mol higher than that for **ii**. Also, overall conformation **ii** is about 2.5 kcal/mol more stable than **i** (for the enediyne).



i **ii**



X	α (°)	E_a (kcal/mol)	α (°)
NH_2,	105	26.9	111
coplanar,	115*	28.8	121*
planar	125	30.7	131
NH_2,	107	31.3	111
perpend.,	117*	29.6	121*
planar	127	27.6	131
BH_2,	111	25.8	117
coplanar	121*	26.1	127*
	131	25.7	137
BH_2,	98	26.6	106
perpend.	108*	26.8	116*
	118	27.0	126

* = optimized value

Figure 2. Activation energies as a function of α, as calculated at BLYP/6-311+G**; See text for details.

reversed for the perpendicular NH_2. The ground state effects are almost exactly the same (ca. 4 kcal/mol) as for the coplanar NH_2, but the transition state shows a much greater destabilization (6 kcal/mol vs 2 kcal/mol) of the smaller α structure, consistent with the postulated in-plane destabilizing orbital interaction. The data for the BH_2 substituent show the opposite trend. For the coplanar geometry, the angle changes have little effect, and no direction. However, for the perpendicular BH_2 orientation, the cyclization barrier decreases as α decreases, consistent with a stabilizing in-plane orbital interaction.

Annulation. The relative enthalpies of the 14 annulated cases we have studied (7 6MR, 6 5MR, and 1 4MR annulations) are given in Table 3. The *d* values for the 3 ring-opening transition states and the 5 medium rings that result therefrom are shown in the structural figures. Also given in Table 3 is the parameter $\Delta r_{1,2}$, which is the increase in the bond length of the "ene double bond" from the starting enediyne to the cyclization transition state; this parameter is discussed with respect to the proposal[14] that its value is related to cyclization rate.

It is seen that benzoannulation produces an enediyne (**9**) that should cyclize at about the same rate as the parent (**1**), in accord with observation; cyclohexadiene-annulated enediyne **48** is somewhat less reactive than **1**, and serves as a reasonable model for annulation without aromatization (as does **23** for the 5MR cases). In accord with the small increase in the observed H atom abstraction barrier for **9p**, the $\Delta E_{(ST)}$ for **9p** is calculated to be 5.3 kcal/mol (6-311+G** basis + ZPVE), which is only 0.2 kcal/mol greater than that for **1p**. Once again, substituent effects are not transmitted, as **45** has the same barrier as **9**.[59] Heteroatom substitution produces very little effect on the calculated cyclization barrier: **10**, **46**, **47**, and **11** all have essentially the same cyclization barriers, and these are at most 1 kcal/mol less than that for **9**. Thus we cannot explain the apparently rapid cyclization of pyrimidine **12**, which we would expect to be quite similar to **46**. The 5MR annulated cases appear to have somewhat greater cyclization barriers than the 6MR ones, although they are similar, except for the positively charged imidazolium fused case (**53**), whose relatively high barrier is reminiscent of the ammonium ion substituent results (**35**).[60] It would appear that the imidazole/imidazolium pair (**52**/**53**) might be useful in terms of changing reactivity with pH. We note that the in-plane lone-pair direct overlap (Figure 1c), which significantly inhibits cyclization for the cases discussed above, is not operative in the annulated cases (e.g., for **10**, **11**, **46**, **47**, or **52**). The difference is that the overlap integrals between the relevant orbitals for the annulated cases are expected to be much

Table 3. Relative Enthalpies (H_{298}, kcal/mol) of Stationary Points for Various Annulated Systems[a]

compd.	enediyne (e)		transition state (t)			p-benzyne[b] (p)	ring-opening transition state (ot)	medium ring "enediyne" (mr)
	H_{rel}	*d* (A)	H_{rel}	*d* (A)	$\Delta r_{1,2}$[c]	H_{rel} (Hrel, SC) [$\Delta E_{(ST)}$)] {r_{ab}(Å)}	H_{rel}	H_{rel}
1	0.0	4.546	27.4	2.078	4.3	14.3 (10.6) [5.1] {2.719}	-	-
9	0.0	4.254	27.5	2.018	6.2	20.4 (16.5) [5.3] {2.734}	26.1	11.0
45	0.0	4.251	27.4	2.015	6.1	-	-	-
10	0.0	4.218	26.9	2.034	6.6	18.6 (14.7) [5.4] {2.755}	-	-
46	0.0	4.286	26.7	2.045	6.2	18.1 (14.1) [6.1] {2.767}	21.3	12.0
47	0.0	4.189	26.4	2.048	7.4	17.1 (13.2) [5.7] {2.784}	ca. 17[d]	5.3
11	0.0	4.138	26.6	2.035	8.8	19.5 (15.5) [6.6] {2.805}	ca. 19[d]	7.2
48	0.0	4.337	28.3	2.049	4.7	15.5 (12.4) [3.6] {2.690}	-	-
49	0.0	4.737	28.8	2.068	4.8	20.4 (16.1) [7.4] {2.780}	-	-
50	0.0	4.631	27.9	2.046	6.4	23.3 (19.1) [10.0] {2.795}	-	-
51	0.0	4.815	29.3	2.063	4.7	21.8 (17.4) [7.9] {2.787}	-	-
52	0.0	4.763	28.6	2.086	4.4	18.9 (14.7) [7.5] {2.800}	-	-
53	0.0	4.864	31.4	2.014	4.0	22.8 (19.0) [5.0] {2.800}	-	-
23	0.0	4.626	27.7	2.099	4.9	14.7 (10.5) [6.6] {2.739}	-	-
54	0.0	5.130	29.9	2.162	3.9	14.8 (11.6) [12.8] {2.800}	14.5	-3.0
59	-	-	-	-	-	- [5.2] {2.737}	-	-

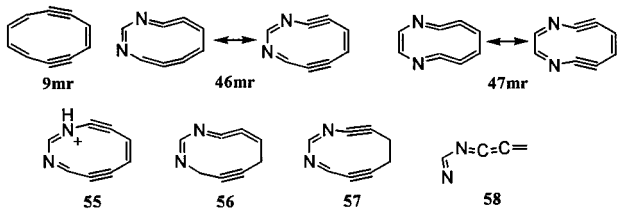
[a] Geometries and thermal rovibrational contributions from the BLYP/6-31G* level, electronic energies from the BLYP/6-311+G** level; absolute enthalpies (298 K, hartrees) for enediynes: **9e**, −384.36674; **10e**, −400.42855; **11e**, −570.05996; **45e**, −483.64460; **46e**, −416.49463; **47e**, −416.48764; **48e**, −385.50591; **49e**, −362.33397; **50e**, −362.33182; **51e**, −378.39075; **52e**, −378.40700; **53e**, −378.75901; **54e**, -308.12519. [b] For the *p*-benzynes, the values are from UBLYP/6-31G* (broken spin symmetry) optimizations and rovibrational corrections, electronic energies from the UBLYP/6-311+G** level; (H_{rel}^{SC}) values are spin corrected; see Table 2 for definitions of H_{rel}(SC), $\Delta E_{(ST)}$, and r_{ab}. [c] $\Delta r_{1,2}$ is the difference in the C_1C_2 bond distances, in pm, between the starting enediyne and its cyclization transition state. [d] These "transition states" are not stationary points on the R surface (see text).

(59) A recent study of several analogues of **45** gave a Hammett ρ value of 0.65. The reactivity range went from 0.8 to 2.8 times as reactive as **9**. This corresponds to an activation free energy decrease of 0.9 kcal/mol to an increase of 0.2 kcal/mol (at 170° C). Since F would fall in the middle of the substituent range studied, essentially no effect calculated is consistent with the experimental findings (Choy, N.; Kim, C.-S.; Ballestero, C.; Artigas, L.; Diez, C.; Lichtenberger, F.; Shapiro, J.; Russell, K. C. *Tetrahedron Lett.* **2000**, *41*, 6955).

(60) A recent synthesis of substituted derivatives of **52** provides the potential to investigate the Bergman cyclization of the imidazole/imidazolium pair (Kim, G.; Kang, S.; Ryu, Y.; Keum, G.; Seo, M. J. *Synth. Commun.* **1999**, *29*, 507).

smaller than those for the nonannulated ones discussed above because the lone-pair vector makes a much more obtuse angle with the radical center vector for the annulated structures.

The $\Delta r_{1,2}$ values show conclusively that the amount of bond lengthening is not related to the activation barrier. Thus the two largest barriers (**53** and **54**) are associated with the *smallest* $\Delta r_{1,2}$ values, but the next smallest value (for **1**) has one of the lower activation barriers. The explanation for the relative reactivities of **5** and **6** lies elsewhere. How, then, might the low reactivities of **5** and **11e** be explained? One possibility is low H atom abstraction reactivity, as found for 9,10-anthracyne.[61] We calculate a $\Delta E(_{ST})$ of 6.6 kcal/mol for **11p,** which is 1.5 kcal/mol higher than that for **1p** at the same level of theory. For the 9,10-anthracyne case, where the H abstraction rate decreased by more than 2 orders of magnitude, we calculate a $\Delta E(_{ST})$ only 0.1 kcal/mol greater than that for **1p** (see the next 2 sections for a more detailed discussion of triplets and H abstraction rates). So possibly low H abstraction rates may be a factor, while these unreactive cases also involve enhanced reversibility, i.e., the intermediate *p*-benzynes are unusually unstable, and cyclorreversion diminishes the rate of enediyne disappearance. It would be necessary that the *p*-benzynes *revert*, rather than open in the opposite direction, as in the aza-enediyne case studied by Chen. Examination of the relative *p*-benzyne energies of the benzannulated (**9p**), pyrimidoannulated (**46p**), pyrazinoannulated (**47p**), and parent (**1p**) cases shows that these annulations are calculated to destabilize the *p*-benzynes by 3−6 kcal/mol, but the reversion barriers are still significant (remember that the experimentally determined reversion barrier for **9p** is 7.4 kcal/mol,[20]). Comparison of the pyrazinyl ring system (**47p**) with the quinoxalyl one (**11p**) indicates that the latter *p*-benzyne is an additional 2.5 kcal/mol less stable; the extra benzene ring causes one of the aromatic rings of **11p** to always have an *o*-quinodimethane resonance structure (the same is true for **5p**), and this may be enough to explain the diminished reactivity of at least **5**. The nonaromatic resonance structure problem (note the longer length of the "annulated ene" double bond, $r_{1,2}$, in these *p*-benzynes) is also evident in the calculated instability of **50p** relative to **49p**, an effect that is clearly not felt in the corresponding transition states.



But an even more significant, surprising effect is operative for **47** and **11**. This became evident when we attempted to R-optimize the *p*-benzynes (**47p** and **11p**). In both cases, 10MR products (**47mr** and **11mr**) were produced by the optimization routine. While the *p*-benzynes were minima on the U surface, attempts to find ring-opening transition states (**47ot** and **11ot**) also failed. It became clear that these do not exist on the RBLYP/6-31G* surface, since structures close to appropriate transition state geometries had energies only slightly above the unrestricted energies for the *p*-benzynes. In other words, the restricted surface just goes downhill from the initial transition states (**47t** and **11t**) to the 10MR products. Of course the real *p*-benzynes are undoubtedly minima, but with rather small barriers to ring opening to the medium rings. Unlike the aza-enediyne case, however, these medium rings are *less stable* than the initial enediynes. And since the conditions are equilibrium producing (i.e., enough energy is being pumped into the system to traverse the highest energy barrier, which is the initial cyclization), the medium rings just revert to starting material. Eventually, the *p*-benzynes bleed off via aromatization, and the entire process is seen as very slow disappearance of the starting material.

Within this group, this behavior is restricted to the cases where two unsaturated nitrogens are connected to the enediyne, and it is worth asking what is special about this situation. Examination of the structures of the medium rings is revealing. It is seen that the bisdehydro[10]annulene **9mr** has an outwardly bowed structure quite similar to that of the cyclic enediynes **13**−**18**. However, as depicted in the line drawing for **46mr** and **47mr** (and shown exactly in Figure 3), the sp^2 nitrogen induces an inward bend, which is clearly associated with the in-plane lone pair on N; elimination of that lone pair via protonation produces **54**, which is structurally virtually identical to **9mr**. Obviously a cumulated resonance structure is possible for these fully conjugated medium ring compounds, so the question arises as to the relative importance of such structures. In an attempt to address this problem, we calculated the structures of enforced cumulene **55**, and acetylene **56**. As shown, the former exhibits more of an inward bend, but this bend is still present in the latter (and even slightly in the acyclic **57**). So while we observe that the bond distances in **46mr** and **47mr** are in accord with a significant cumulenic contribution, the main factor in causing the inward bend appears to be the in-plane N lone pair. However, stabilization comes with having the N in position to be at the terminus of a cumulated structure, since **47mr** is 2.3 kcal/mol lower in enthalpy than **46mr** (a situation that is reversed for the relevant **e**, **t**, and **p** structures).

Armed with an understanding of **11** and **47**, we suspected that Schreiner's failure to find a cyclization transition state for **54mr** (to **54p**) was due to a similarly low barrier from **54p** (and/or an unusual transition state structure). We readily obtained the U-optimized structure for **54p**, but subsequent calculations revealed that this was indeed an unusual case. First of all, the frequency calculation on **54mr** revealed that it was a transition state, but the slightly twisted minimum was only *4 cal/mol* lower. Inclusion of the rovibrational corrections placed the C_{2v} structure 0.6 kcal/mol below the twisted one. Obviously the twisting relieves torsional strain, while exacerbating acetylenic bending strain. The reason this may be of more than a passing theoretical amusement is that it is possible that the inactive form of some natural enediynes, such as the apoprotein incarcerated C-1027, may be inactivated, in part, by twisting of the acetylenes with respect to each other. Second, we were surprised to find that R-optimization of **54p** also produced a stable structure, as this meant that a transition state between **54p** and **54mr** could be located. Interestingly, the restricted **54p** structure is calculated to be 0.2 kcal/mol *below* the unrestricted one at the 6-311+G** level (and only 0.3 kcal/mol above at the 6-31G* level). The energetic similarity between U and R structures is reminiscent of the 3-aza-enediyne case, as is the large calculated $\Delta E(_{ST})$ (12.8 kcal/mol at 6-311+G** + ZPVE vs 14 kcal/mol for the aza-enediyne). An additional similarity is that the more stable enediyne (**54mr**) is reached by the lower transition state (**54ot**), unlike the situation for the **11**/**47** pair. As shown in Table 3, the enthalpy of **54ot** at the 6-311+G** level actually falls below that of **54p**, although it is 1.1 kcal/mol higher at 6-31G*. Transition state **54ot** has an unusually short $d = 1.786$ Å. Of interest with respect to possible drug

(61) Schottelius, M. J.; Chen, P. *J. Am. Chem. Soc.* **1996**, *118*, 4896.

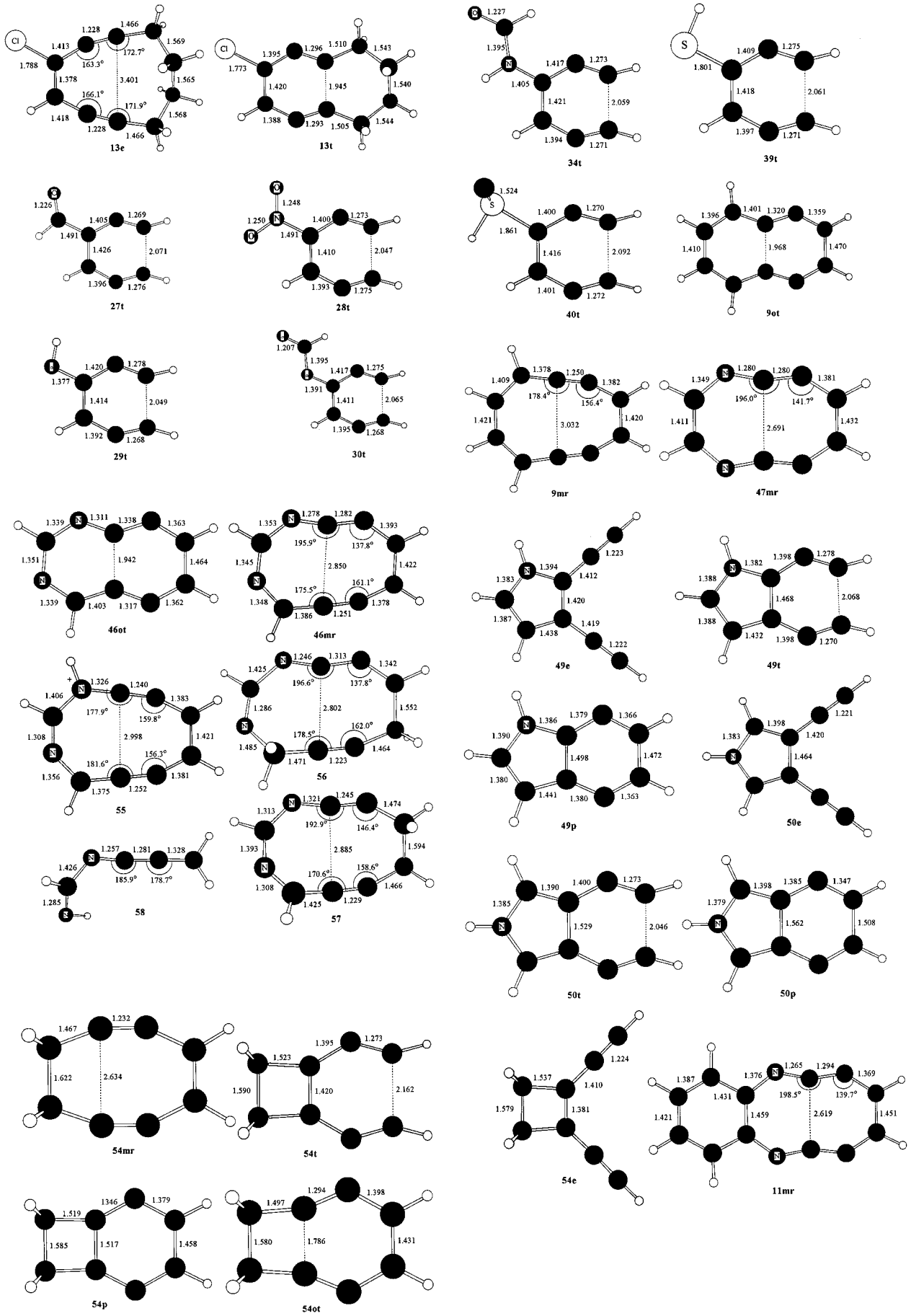
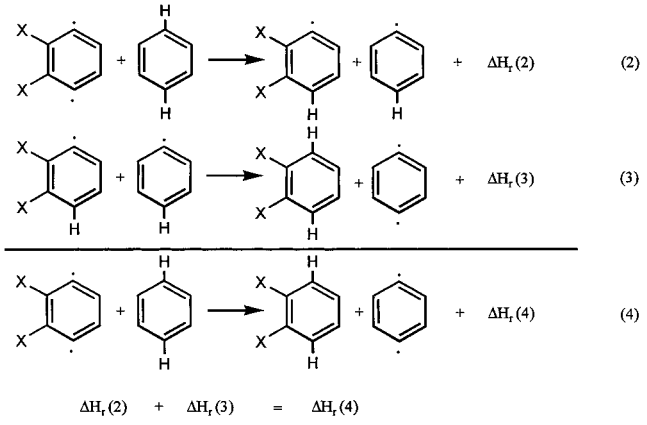


Figure 3. Ball and stick drawings of selected enediynes (**e**), transition states (**t**), and *p*-benzynes (**p**).

design is the relatively high barrier between **54e** and **54p**. The 4MR is more effective at raising the cyclization barrier than is a single halogen. Finally, the energy difference between **54e** and **54mr** is quite small, with **54e** being much less disfavored than the ca. 15 kcal/mol indicated by PM3 semiempirical theory.

The Singlet−Triplet Energy Gap. Tables 2 and 3 contain the singlet−triplet energy gaps for 28 of the *p*-benzynes reported herein. As can be seen in the former table, expectations[59] that σ electron withdrawal would decrease the singlet−triplet gap are confirmed. That it is a σ effect is seen by noting that ΔE_{ST} decreases in the order $CH_3 > NH_2 > OH > NO_2 \sim NH_3^+$; concomitant bond distance effects are also apparent (see Figure 3). Also, the prediction that compression of the radical−radical distance (r_{ab}) would increase through-space interaction, and thus lower the ΔE_{ST}, holds for homologous compounds, e.g., for **48p**, **1p**, **23p**, and **54p**, where the r_{ab} and ΔE_{ST} values increase together. Otherwise, however, other factors overcome the distance effect. For example, **11**, **50**, **53**, and **54** have about the same r_{ab}, but widely divergent ΔE_{ST} values. Also **20** and **22** have similar ΔE_{ST} values, but fairly different r_{ab} values, with the shorter r_{ab} corresponding to the larger ΔE_{ST}. Finally, the notion that asymmetric *p*-benzynes, as in the natural products, would have larger singlet−triplet splittings because the radical orbital degeneracy would be broken does not seem to hold (much as Woodward−Hoffmann "orbital symmetry" rules are not restricted to symmetric systems). For example, methyl-*p*-benzyne (**26p**) has a smaller splitting than the parent (**1p**) or the symmetrically dialkylated benzyne **23p**. Also, unsymmetrical benzynes **10p** and **46p** have about the same or smaller splittings than symmetrical **9p**, **11p**, **47p**, and **59**. And the largest splitting encountered herein is for symmetrical cyclobuta-*p*-benzyne, **54p**.



H Atom Abstraction and the Singlet−Triplet Gap. As mentioned earlier, the singlet−triplet gap, which is enhanced by singlet stabilization via both through-space and through-bond effects, is thought to be reflective of singlet *p*-benzyne reactivity, with a small gap indicating relatively greater reactivity. Although qualitatively appealing, one might question the quantitative application of this idea. In fact, careful evaluation of Roth's data for the kinetics of **1** and **9** reveals that **9** has an approximately 0.6 kcal higher enthalpic barrier to H abstraction, but this is overcome by entropic effects, to where **9p** reacts more rapidly than **1p** with MeOH, and at about the same rate as the phenyl radical.[20] Hirama's apparently contradictory observation that the H abstraction step is kinetically important for the cycloaromatization of **9** (whereas it is not for **1**) may be due to the fact that his results are for abstraction from the much more reactive 1,4-cyclohexadiene, where an earlier transition state may alter the entropic picture. The other relevant observation is the 100−200-fold rate decrease for H abstraction from

Table 4. Enthalpies of Reactions 2, 3, and 4 and Singlet−Triplet Splittings for Selected *p*-Benzynes[a]

p-Benzyne	ΔH_r (2)	ΔH_r (3)	ΔH_r (4)	$\Delta E_{(ST)}$	r_{ab}(Å)	Hfs (G)[d]
1p	2.8[b] (4.7)[c]	-2.8	0.0	5.1 (3.8)[c]	2.719	2.4 (1.9)
20p	-2.7	-5.2	-7.9	0.5	2.713	0.2
23p	4.4	-2.5	1.9	6.6	2.739	2.9
54p	8.9	-2.4	6.5	12.8	2.800	5.0
9p	3.1	-2.9	0.2	5.3	2.734	2.4
59	3.1	-3.2	-0.1	5.2	2.737	2.3
50p	6.9	-2.5	4.4	10.0	2.795	4.1
11p	3.5	-3.8	-0.3	6.6	2.805	2.2
53p	-1.1	-7.0	-8.1	5.0	2.800	2.5

[a] Reaction enthalpies calculated at BLYP/6-31G*; singlet−triplet gap calculations are for electronic energies at BLYP/6-311+G** and BLYP/6-31G* ZPVE corrections; all energies in kcal/mol; absolute enthalpies of relevant arenes and radicals (hartrees): phenyl, −231.36289, benzene, −232.02913; 2,3-difluorophenyl, −429.83392, *o*-difluorobenzene, −430.50414; α-indanyl, −347.96676, indan, −348.63253; α-cyclobutaphenyl, −308.67012, cyclobutabenzene, −309.33571; α-naphthyl, −384.89383, naphthalene, −385.56039; 9-anthryl, −538.41925, anthracene, −539.08619; α-isopyrrolophenyl, −362.84639; [*bc*]benzopyrrole, −363.51220; α-quinoxalyl, −570.54263, quinoxaline, −571.21053; α-imidazolium-phenyl, −379.29189, benzoimidazolium ion, −379.96477. [b] The report of this value as −4.2 at the same level of theory in ref 12 is due to that author's use of R-optimized geometry and energy for **1p**, whereas we use U values throughout. [c] Experimental values as reported in ref 51. [d] Hyperfine splitting constants, calculated at the UBLYP/6-311+G** level, for the *p*-H of the radical formed by adding an H to one of the radical centers in the *p*-benzyne, i.e., the radicals of eq 3, the energies for which are given in footnote *a* above; the only known experimental value is given in parentheses (ref 64).

^{i}PrOH and MeCN by 9,10-anthracyne (**59**) relative to the phenyl radical, although the temperature dependence was not measured. Our calculated ΔE_{ST} for **59** is 5.2 kcal/mol, right between that for **1p** (5.1) and **9p** (5.3). Another way to relatively easily evaluate the H abstraction capability of a *p*-benzyne is to calculate the enthalpy of reaction of isodesmic eq 4, as has been performed by several authors.[12,62] A better assessment should derive from the first abstraction step, eq 2, but this requires the more demanding calculation of radical energies.[63] Table 4 reports the reaction enthalpies of eqs 2−4 for 9 *p*-benzynes. If eq 4 is to give an adequate approximation of eq 2, then the reaction enthalpies of eq 3 must remain constant. The results show that this notion holds well for the hydrocarbon cases, but not so well for heterosubstituted cases **20p**, **11p**, and **53p**. It remains to be determined whether direct calculations of H abstraction activation barriers will confirm the "discrepancies" for heterosubstitution.

An alternative is that the singlet−triplet gaps have been miscalculated at the DFT level of theory. Cramer and Squires[64] showed that the DFT-calculated radical hyperfine coupling of the H in the position where removal would give the aryne correlated well with the singlet−triplet splitting calculated with

(62) Kraka, E.; Cremer, D. *J. Am. Chem. Soc.* **2000**, *122*, 8245.

(63) Of course the best approach would be to calculate the energy of the transition state for abstraction, which has been attempted for only the parent case.[48]

(64) Cramer, C. J.; Squires, R. R. *J. Phys Chem. A* **1997**, *101*, 9191. We thank a referee for suggesting this singlet−triplet gap test.

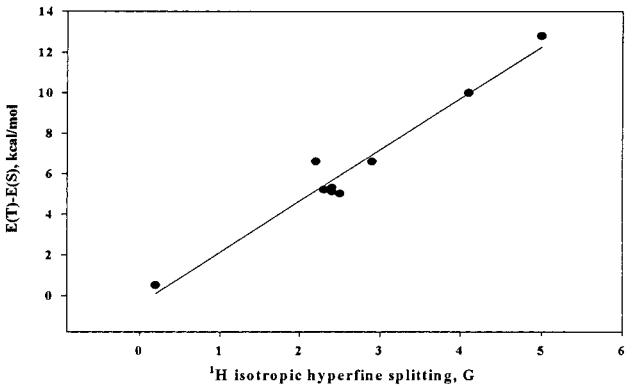
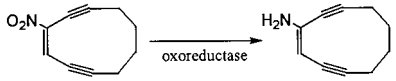


Figure 4. BLYP *p*-benzyne singlet−triplet splittings for the arynes of Table 4 vs BLYP/6-311+G** hfs for the corresponding monoradicals ($R^2 = 0.96$).

CASPT2 ($R^2 = 0.97$ for benzynes and naphthalynes). Figure 4 shows the results for the 9 cases given in Table 4. The correlation coefficient ($R^2 = 0.96$) shows that the DFT singlet−triplet gaps are reliable. The only point appreciably off the correlation line is for *p*-indanyne (**23p**), where the singlet−triplet gap appears to be overestimated. In any event, the heterosubstituted cases mentioned above have well-correlated singlet−triplet gaps.

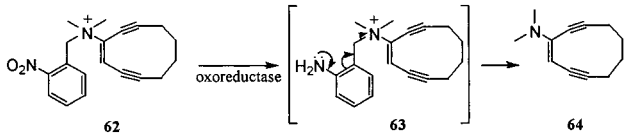
Conclusions and Applications

DFT calculations effectively explain the observed retardation of enediyne cycloaromatization induced by vinylic chlorine substitution: that retardation is due to an increased cyclization barrier. Furthermore, calculations on a variety of vinyl-substituted cases indicate that σ-electron withdrawal inhibits cyclization. We also show that through-space overlap of a substituent orbital with the developing *p*-benzyne radical center has an important effect on cyclization rates. Studies of annulated



60 **61**

enediynes revealed relatively small effects on cyclization rates, but sometimes dramatic effects on *p*-benzyne H abstraction vs retro- or forward Bergman reaction rates. In particular, neighboring unsaturated nitrogen can facilitate forward ring opening to medium rings with cumulenic resonance structures. We were also able to delineate the complete Bergman cyclization pathway for 1,2-diethynylcyclobutene.



62 **63** **64**

On the basis of the findings reported herein, our current objective is to exploit electronic effects at the vinyl position to design bona fide prodrugs which undergo activation under cellular conditions. One possibility would be 3-nitrocyclodeca-3-ene-1,5-diyne (**60**), which could undergo reduction to give more reactive 3-aminocyclodeca-3-ene-1,5-diyne (**61**). Precedent exists for such transformations in hypoxic tumor cells, providing an inbuilt selectivity index.[65] Another possibility would be to utilize the reduced reactivity of a quaternary aminoenediyne, such as **62**, which would be expected to undergo bioreductive elimination to **63** under hypoxic conditions, resulting in spontaneous release of the free (and more reactive) amine **64**. We anticipate that our recently developed route to chloroenediynes will facilitate many of the proposed prodrug syntheses,[26] either by metal−halogen exchange and subsequent coupling or direct addition of organometallic reagents.

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Supporting Information Available: Tables of Cartesian coordinates and energies for all optimized stationary points (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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