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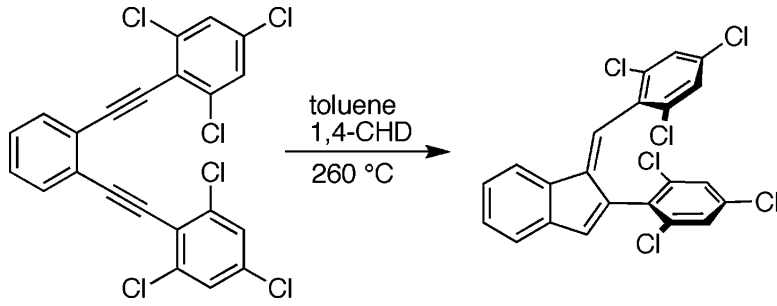

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Thermal C^1-C^5 Diradical Cyclization of Enediynes

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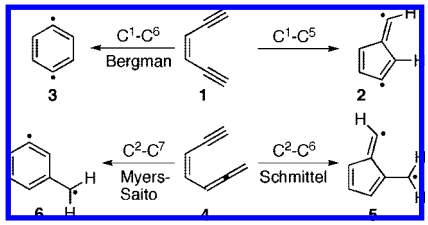
Thermal cycloaromatizations of enediynes (Bergman, C^1-C^6)[1] and enyne-allenes (Myers-Saito, C^2-C^7)[2] (Scheme 1) are of interest because their diradical intermediates provide the mode of action of natural enediyne antitumor antibiotics.[3] In 1995 Schmittel found an alternative diradical cyclization of enyne-allenes (C^2-C^6)[4] leading to fulvene diradical intermediates,[5] and these also have been shown to cleave DNA in vitro.[6]

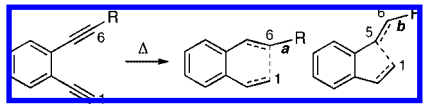
Scheme 1. Thermal Cyclizations of Enediynes and Enyne-Allenes



The thermal C^1-C^5 diradical cyclization of enediynes, a regiovariant of the well-known Bergman cyclization, is not well documented, if at all,[7] but the C^1-C^5 cyclization of enediynes initiated by either photoinduced electron transfer,[8] electrophiles,[9] radicals,[10] or metals[11] is known. For the parent enediyne **1**, computational studies by Schreiner found a much higher barrier for the C^1-C^5 diradical cyclization than for the C^1-C^6 pathway: 41.0 vs 25.2 kcal/mol at the BLYP/6-31G(d) level of theory (42.1 vs 27.1 kcal/mol for BCCD(T)/cc-pVDZ single points at the BLYP geometries).[12] However, in the present work we show that this preference can be reversed and the thermal C^1-C^5 diradical cyclization is an important, and sometimes the major, reaction in diaryl-substituted enediynes.

To evaluate the feasibility of C^1-C^5 cyclization, we computationally screened several benzannulated enediynes substituted with an aryl group at one alkyne terminus, and the results are summarized in Table 1.[13] From entries **7a** and **7b**, it is seen that the activation energy for Bergman cyclization increases by 4 kcal/mol when the hydrogen atom is replaced by a phenyl group (likely a steric effect), but for the C^1-C^5 pathway it *decreases* by 6 kcal/mol. The latter effect is due to stabilization of the emerging vinyl radical center in the C^1-C^5 pathway, and is evident in the short phenyl-C^6 bond (bond ***b***) in the transition state (TS). Such effects do not operate in the Bergman pathway, but the C^1-C^6 cyclization remains strongly preferred for **7b**. However, when a 2,6-dichlorophenyl group is substituted for phenyl (**7c**), increased steric effects (small in the C^1-C^5 pathway) further slow the Bergman reaction, and the competing TSs are brought to within 1 kcal/mol. That this is a steric effect, and not an electronic effect of the chlorines, is evident from similar results found when a 2,6-dimethylphenyl group (**7f**) is employed instead. Addition of either a nitro (**7d**) or an amino group (**7e**) to the aryl ring makes the activation energies of the C^1-C^6 and C^1-C^5 cyclizations essentially equal at this level of theory. Finally, a higher-level calibration of these calculations is given by BCCD(T)/cc-pVDZ//RBLYP/6-31G(d) energies for the reactions of **7c**, yielding E_a values of 31.1 and 35.3 kcal/mol for the C^1-C^6 and C^1-C^5 cyclizations, respectively, suggesting that the RBLYP calculations may somewhat underestimate the barrier to the C^1-C^5 process.[13]

Table 1. ZPE-Corrected RBLYP/6-31G(d) Activation Energies[a] (kcal/mol) for the Cyclizations of Monosubstituted 1,2-Diethynylbenzenes



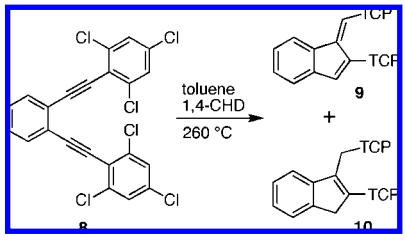
R	E_a (C^1-C^6)	E_a (C^1-C^5)	*a*, *b* (Å)
H (**7a**)	24.6	37.2[b]	
phenyl (**7b**)	28.7	31.4	1.459, 1.406
2,6-dichlorophenyl (**7c**)	30.8	31.6	1.462, 1.400
2,6-dichloro-4-nitrophenyl (**7d**)	31.8	31.6	1.458, 1.395
2,6-dichloro-4-aminophenyl (**7e**)	30.7	30.4	1.459, 1.398
2,6-dimethylphenyl (**7f**)	30.5	30.9	1.471, 1.406

[a] See note 13. [b] BS-UBLYP/6-31G(d), ref 12a.

For an experimental test of the thermal C^1-C^5 cyclization, we chose compound **8**, a benzannulated enediyne with 2,4,6-trichlorophenyl (TCP) groups at both alkyne termini. Not only is the synthesis of **8** convenient (Sonogashira coupling of 1,2-diiodobenzene and 2,4,6-trichlorophenylacetylene[14] gives **8** in 50% yield), but also the addition of the second TCP group should further impede the Bergman cyclization.

DSC measurements on neat enediyne **8** showed the onset of reaction at about 250 °C. Thermolysis of **8** in toluene at 260 °C in the presence of 1,4-cyclohexadiene gave indene derivatives **9** and **10** (Scheme 2) in 19% and 50% isolated yield, respectively, after purification by supercritical fluid chromatography. The

Scheme 2. Thermolysis of Enediyne **8**



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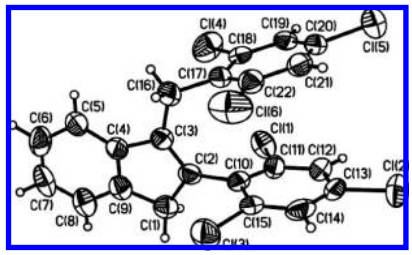

Figure 1. X-ray structure of indene **10**.

structures of **9** and **10** were determined from ^{1}H NMR, ^{13}C NMR, and HRMS data, and the structure of **10** was established by X-ray crystallography (Figure 1). The observed products **9** and **10** apparently arise from the C^1-C^5 cyclization of enediyne **8**; interestingly, no Bergman cyclization product was observed in these reaction mixtures.[15] Thermolyses at 210 °C returned unchanged **8**.

When thermolyses of **8** were conducted in toluene or toluene-d_8, at 260 °C in the absence of 1,4-CHD, the yields of **9** and **10** were greatly reduced,[16] and again no Bergman products were observed. Significantly, in the case of the toluene-d_8 reaction, GCMS analysis found substantial deuterium incorporation in compound **9** (34% d_2, 51% d_1, 15% d_0). These results are fully consistent with C^1-C^5 cyclization via a diradical intermediate (**14c**, Scheme 3) analogous to **2**.

This is not the first thermal reaction reported to yield C^1-C^5 cyclization products. In one very special case, a relatively strained macrocyclic enediyne underwent C^1-C^5 cyclization to an indenoindene, possibly via a diradical intermediate.[12a,17] Of greater relevance is Matzger's study[7] of Bergman cyclizations of 1,2-bis(phenylethynyl)benzene (**11**, Scheme 3), where he noted, "Remarkably, benzofulvenes and their hydrogenation products were detected in the product mixture in yields of up to 2% and ~10%, respectively. Although direct five-membered ring cyclization may be occurring, the majority of these products likely arise by radical attack processes as evidenced by the higher yields realized at lower temperatures in combination with higher CHD concentrations." In concert with the latter statement, Schreiner has cautioned[9c] that "the thermal cyclization [of **11**] yielding [**14**] is unlikely because of the high barrier for cyclization (ca. 40 kcal/mol at UBS-B3LYP/6-31G*)..." *This is the central question:* is it really necessary to invoke radical attack processes for the formation of indenes in such reactions, or is the direct formation of a C^1-C^5 cyclized, diradical intermediate an easily accessible pathway when favored by both electronic and steric effects, as in diaryl-substituted enediynes **8** and **11**? Our present results argue strongly in favor of the latter conclusion.

Scheme 3. Thermal Cyclization Paths for 1,2-Bis(arylethynyl)benzenes, and Other Related Compounds

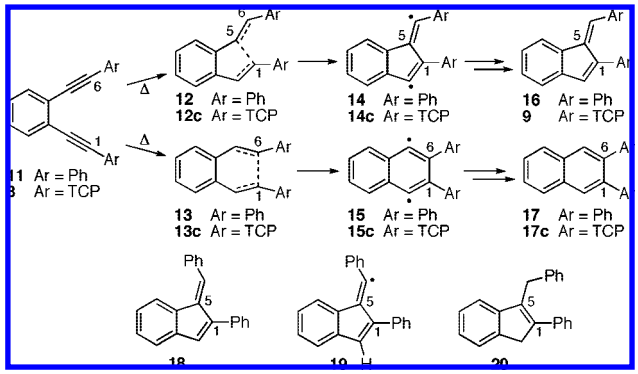

Table 2. ZPE-Corrected Activation Energies (kcal/mol) for the Thermal Cyclizations of 1,2-Bis(arylethynyl)benzenes

	enediyne 11		enediyne 8	
level	C^1-C^5 (TS **12**)	C^1-C^6 (TS **13**)	C^1-C^5 (TS **12c**)	C^1-C^6 (TS **13c**)
BLYP/6-31G(d)//BLYP/6-31G(d)	36.3	38.5	38.7	43.2
BCCD(T)/cc-pVDZ//-BLYP/6-31G(d)	35.1	32.9		

First, the computational data of Table 1 predict that the C^1-C^5 and C^1-C^6 cyclizations should become competitive upon addition of an aryl group to even one alkyne terminus, due to both the mesomeric stabilization of the C^1-C^5 TS and steric destabilization of the C^1-C^6. Computational studies of the reactions of the experimentally investigated enediynes **8** and **11** further strengthen this conclusion (Table 2). At the BLYP/6-31G(d) level,[13] the C^1-C^5 cyclization of hydrocarbon **11** is actually favored by 2.2 kcal/mol over the C^1-C^6, and for the chlorinated compound **8**, the C^1-C^5 cyclization is favored by a full 4.5 kcal/mol! Most of the latter difference is due to steric destabilization of the Bergman cyclization TS, as illustrated in Figure 2. Bulky terminal substituents tend to inhibit the C^1-C^6 reaction,[12a] because these groups must be brought together to flank the newly forming bond, but such steric effects are smaller for C^1-C^5 cyclizations in which the substituents are separated by one more atom. However, the Bergman cyclization of compound **8** is particularly unfavorable, because the C^1-C^6 TS structure contains two tight chlorine−chlorine contacts (3.59 Å each; the sum of the van der Waals radii is 3.8 Å). In the C^1-C^5 TS structure the closest chlorine−chlorine contact distance is 3.92 Å.

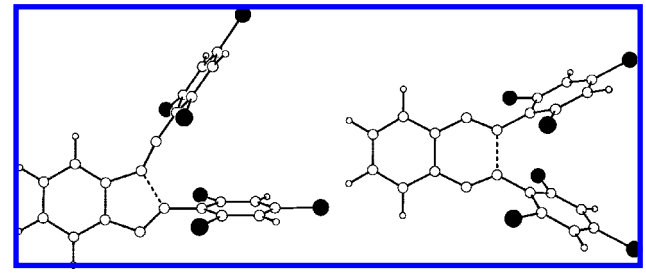

Figure 2. BLYP/6-31G(d)-calculated TS structures for the C^1-C^5 (left) and C^1-C^6 (right) cyclizations of compound **8**.

Once again, high-level calibration of these DFT calculations was provided by BCCD(T)/cc-pVDZ single points for the reactions of **11** (Table 2). These placed the Bergman cyclization TS 2.2 kcal/mol below the C^1-C^5 TS (rather than 2.2 kcal/mol above, as found by the DFT methods). Extrapolating from these results, the C^1-C^5 cyclization should still be slightly favored for compound **8**.

How do these computational studies match the available experimental data? The formation of only C^1-C^5 cyclization products upon thermolysis of **8** fits nicely with the DFT results in Table 2. Equally significant is Matzger's carefully tabulated data[7] for the thermolysis of **11**, which show that although Bergman cyclization gave rise to the major products in his reaction mixtures, C^1-C^5 cyclization products were always present in significant amounts. The C^1-C^6 to C^1-C^5 ratio was typically ~5:1, suggesting that in reality the C^1-C^6 TS is favored by 1.8 kcal/mol (at 300 °C) over the C^1-C^5, a finding that is in excellent agreement with the BCCD(T)/cc-pVDZ calculations for the reactions of **11**.

However, Matzger (and a referee) are of the opinion that the C^1-C^5 cyclization products in such reactions are due to transfer

hydrogenations involving 1,4-CHD, which is routinely added as a hydrogen source in order to prevent the polymerization of diradicals. (Indeed, yields of *both* C^1-C^6 and C^1-C^5 cyclization products increase with increasing levels of 1,4-CHD.[7]) For this reason, we sought evidence of C^1-C^5 cyclization under conditions where transfer hydrogenation is unlikely.

Certainly, the formation of **9** upon thermolysis of **8** in the *absence* of 1,4-CHD, as well as the incorporation of two deuterium atoms in a substantial fraction of the molecules when **9** is produced in toluene-d_8, argue that these products, at least, do not result from transfer hydrogenations.

Even stronger evidence of a thermal C^1-C^5 cyclization is provided by thermolyses of compound **11** at much lower temperatures than employed by Matzger. The activation energies of Table 2 suggest that the C^1-C^5 reaction might have a measurable rate even below 200 °C, and indeed, thermolysis of **11** in toluene at 180 °C for 17 h gave ca. 0.2% conversion to (*Z*)-1-benzylidene-2-phenyl-1*H*-indene (**16**), 0.2% 2,3-diphenylnaphthalene (**17**), and, interestingly, no detectable (*E*)-indene **18**, as judged by GC−MS analysis of the reaction mixtures with authentic standards of each compound for comparison.[18] The significance of this experiment is twofold. First, a chain transfer hydrogenation at such a low temperature without 1,4-CHD is highly unlikely. Second, the observed (*Z*)-isomer **16** is the main product expected from a thermal C^1-C^5 cyclization, but the (*E*)-isomer **18** would be the principal product from a transfer hydrogenation.[19] However, when 1,4-CHD is included in the thermolysis of **11** at 180°, compounds **16** (1.3%) and **17** (0.2%) *as well as* **18** (0.2%) and the tetrahydro product **20** (0.3%) are observed, an indication that transfer hydrogenation may now occur.[19]

The simplest interpretation of the aggregate computational and experimental data is that enediynes **8** and **11** do undergo thermal C^1-C^5 diradical cyclizations, although transfer hydrogenation likely contributes to the formation of C^1-C^5 cyclization products in the presence of 1,4-CHD.

The mechanistic features that result in the switch from a C^1-C^6 to a C^1-C^5 pathway—stabilization of the evolving diradical intermediate in the C^1-C^5 pathway and a steric conflict between substituents on the alkyne termini in the Bergman TS—are precisely the features also responsible for the switch from the Myers-Saito to the Schmittel cyclization of enyne-allenes.[4,5a] Thus, there is ample theoretical and experimental evidence that C^1-C^5 diradical cyclizations can be observed in the thermal reactions of enediynes.

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Supporting Information Available: Synthetic procedures, ^{1}H and ^{13}C NMR spectra for **8**−**10**; a crystallographic information file (CIF) for **10**; GC−MS data for deuterium incorporation into **9**; and an ASCII text file containing calculated coordinates of enediynes **7b**−**f**, **8**, and **11**, C^1-C^5 and C^1-C^6 cyclization transition states for **7b**−**f**, and cyclization transition states **12**, **12c**, **13**, and **13c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) At the RBLYP/6-31G(d) level of theory, most C^1-C^5 cyclization diyls (e.g., **2**) are not potential minima; however, the monoaryl diyls *are* shallow minima, and thus computational TSs (Table 1) leading from enediynes **7b**−**f** to the C^1-C^5 diyls can be located by using TS search algorithms in Gaussian 03. (We have used similar RBLYP calculations for the design of substrates for diradical cyclizations; see: Semmelhack, M. F.; Wu, L.; Pascal, R. A., Jr.; Ho, D. M. *J. Am. Chem. Soc.* **2003**, *125*, 10496–10497.) For the location of both the C^1-C^5 and C^1-C^6 cyclization diaryl diyls, as well as the C^1-C^5 TS structures (Table 2), the BS-UBLYP/6-31G(d) method recommended by Schreiner[12a,c] was employed. All reported DFT activation energies include ZPE corrections from frequency calculations at the same level. Activation energies obtained from BCCD(T)/cc-pVDZ single-point calculations at RBLYP/6-31G(d) or BS-UBLYP/6-31G(d) geometries (again following Schreiner[12a,c]) include RBLYP or BS-UBLYP ZPE corrections, respectively.
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(15) GC−MS analyses of the crude reaction mixtures found no compounds with the formula $C_{22}H_{10}Cl_6$ other than **9**, and the characteristic naphthalene resonances of a Bergman cyclization product were not observed in the ^{1}H NMR spectra of the mixtures. Reduction of **9** to **10** is well precedented for similar systems.[7,8b]
(16) C^1-C^5 cyclization products made up 15−35% of the volatile chlorinated products, and **8** was entirely consumed, but because of polymer formation in the absence of 1,4-CHD, the absolute yields were only 0.5−1.5%.
(17) Chakraborty, M.; Tessier, C. A.; Youngs, W. J. *J. Org. Chem.* **1999**, *64*, 2947–2949.
(18) **17** is commercially available, **16** (along with **17**) was prepared by TPP-sensitized photolysis of **11**,[8a] **18** was prepared by Bu_3SnH-induced radical cyclization of **11**,[8b] and a mixture of **16** and **18** (and many other products) was generated by lithium naphthalide reduction of **11**.[9b]
(19) At the BLYP/- and B3LYP/6-31G(d) levels, (*E*)-isomer **18** is more stable than (*Z*)-isomer **16** by ∼1.5 kcal/mol; thus the excess of **16** reflects a nonequilibrium mixture of products. Bu_3SnH-induced cyclization of **11** gives predominantly **18**,[8b] and one would expect transfer hydrogenations to do the same. Further, at the BS-UBLYP/6-31G(d) level, only the (*Z*)-isomer of diyl **14** is a minimum, and at the UBLYP/6-31G(d) level, only the (*E*)-isomer of H-atom addition product **19** is a minimum (although both have wide C^5-C^6-Ar bond angles). To the extent that the structures of these radicals are reflected in the products' stereochemistry, the formation of less stable **16** is an indicator of diradical cyclization.

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