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1,4-Addition of Benzene to a Dihydrocyclopent[*a*]indene Diradical: Synthesis and DFT Study

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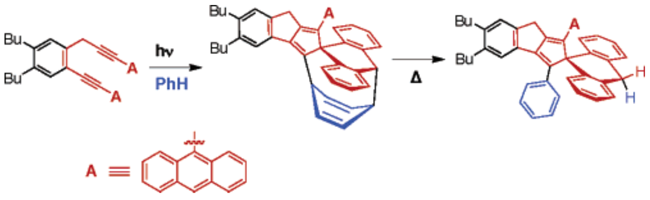
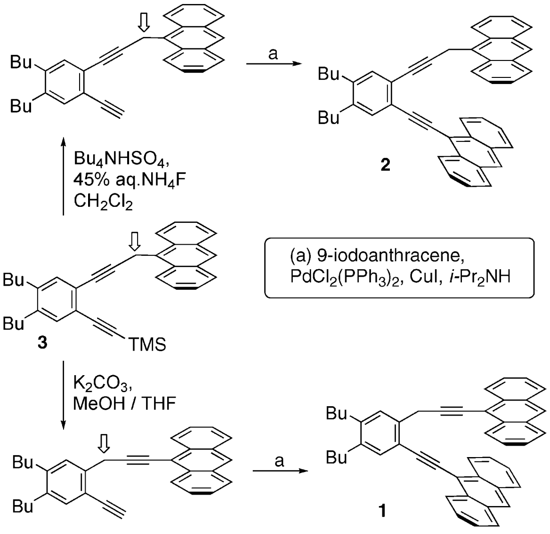
Received August 24, 2004



Photochemical cyclization of compound **1**, a *homo*enediyne $(-\mathrm{CCC{=}C}CH_2\mathrm{CC}-)$ bearing two ethynylanthracene chromophores, yields two isomeric dihydrocyclopent[*a*]indene ring systems, spiro-fused to the 9-position of a 9,10-dihydroanthracene moiety. Evidence of a photochemically initiated diradical cyclization pathway is proposed on the basis of (i) hydrogen abstraction from reaction with 1,4-cyclohexadiene (1,4-CHD) and (ii) the observation of 1,4-addition of benzene (solvent). The reaction was further analyzed by a complete density functional theory (DFT) study, using an unrestricted approach (UBLYP) with a 6-31G* basis set for the open-shell triplet states of the reactants, products, and diradical intermediates to model the photochemical nature of observed transformation. A mechanism detailing the observed cyclization/addition reaction is proposed.

Herein we report the synthesis, chemical reactivity, and density functional theory (DFT) analysis of an enediyne[1] *homologue* $(-\mathrm{CCCH{=}CHCH_2CC}-)$, dianthracene-*homo*-enediyne **1**. Homoenediyne **1** and enediyne **2** can each be selectively prepared from the trimethylsilyl deprotection of terminal alkyne **3** (Scheme 1). Photochemical cyclization[2,3] of compound **1** yields two isomeric dihydrocyclopent[*a*]indene ring systems, spiro-fused to the 9-position of a 9,10-dihydroanthracene moiety, compounds **4** and **5**. Evidence of a diradical pathway is gleaned both from photochemical reaction of compound **1** with 1,4-cyclohexadiene (1,4-CHD) and benzene (solvent). The two isomeric photoproducts resulting from benzene addition, compounds **4** and **5**, are found to be thermally labile and isomerize to give compounds **6-T** and **7**, respectively. In total, the photochemical cyclization/addition reaction of compound **1** and benzene provided a 70% combined yield of compounds **4** and **5**. Given that the photocyclization chemistry observed for compound **1** is *not observed* for compound **2**, only the chemistry related to compound **1** is reported in this paper.

SCHEME 1



The divergent synthesis leading to both compounds **1** and **2** is shown in Scheme 1. As stated, the branching point is defined by the method of trimethylsilane (TMS) deprotection of synthetic intermediate, compound **3**. TMS deprotection of compound **3** with K$_2$CO$_3$/MeOH−THF proceeds with an unanticipated isomerization of the alkyne moiety, effectively inserting a methylene unit into the original enediyne scaffold (compound **1**).[4] Conversely, TMS deprotection using buffered conditions (Bu$_4$NHSO$_3$, 45% aq NH$_4$F) proceeds without isomerization to provide compound **2**.

Initial studies subjected homoenediyne **1** to irradiation (1000 W; >400 nm) in degassed (a) 1,4-CHD and (b) neat benzene. The crude reaction mixtures were analyzed by

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[1] For leading papers and reviews of enediyne chemistry, see: (a) Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660. (b) Nicolaou, K. C.; Dai, W. M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387. (c) Nicolaou, K. C.; Smith, A. L. *Acc. Chem. Res.* **1992**, *25*, 497. (d) Grissom, J. W.; Gunawardena, G. U.; Klingberg, D.; Huang, D. H. *Tetrahedron* **1996**, *52*, 6453.

[2] (a) For a comprehensive list of nonthermal initiation of enediyne cyclizations published prior to 1997, see ref 2c. For some more recent examples, see the following, as well as references therein: (b) Theory: Kraka, E.; Cremer, D. J. *J. Am. Chem. Soc.* **2000**, *122*, 8245. Photochemical cyclization: (c) Evenzahav, A.; Turro, N. J. *J. Am. Chem. Soc.* **1998**, *120*, 1835. (d) Funk, R. L.; Young, E. R. R.; Williams, R. M.; Flanagan, M. F.; Cecil, T. L. *J. Am. Chem. Soc.* **1996**, *118*, 3291; (e) Chemical-induced cyclization: Rawat, D. S.; Zaleski, J. M. *J. Am. Chem. Soc.* **2001**, *123*, 9675.

[3] For a comprehensive review of anthracene photochemistry, see: Becker, H. D. *Chem. Rev.* **1993**, *93*, 145.

[4] Newman-Edwards, R. H.; Simon, R. J.; Carpenter, B. K. *J. Org. Chem.* **1990**, *55*, 695−711.

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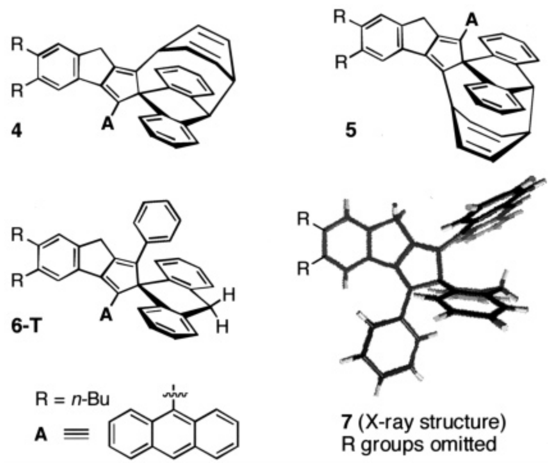

FIGURE 1. Compounds **4**, **5**, **6-T**, and **7**.

GC−MS. Reaction mixture "**a**" revealed a 4:1 composition of products with masses equal to $\mathbf{1}\cdot H^+$ and $\mathbf{1}\cdot H^+ + 2$, the latter mass being consistent with a diradical intermediate abstracting two H-atoms from 1,4-CHD.

Analysis of reaction mixture "**b**" (1000 W; >400 nm; degassed benzene; 48 h; 18 °C; nitrogen atmosphere) revealed four major products (compounds **4**, **5**, **6-T**, and **7**, vide infra) exhibiting closely valued R_f's (as determined by thin-layer chromatography). Mass spectrometric analysis revealed all four to be isomers with a mass equal to starting material (compound **1**) plus benzene.

During isolation and purification of products from reaction "**b**", it became evident that only two of the four isomers were immediate photoproducts (compounds **4** and **5**; Figure 1). The remaining two isomers likely resulted from subsequent thermal rearrangement (compounds **4** → **6-T** and **5** → **7**; Figure 1). Although thermal instability complicated isolation and characterization, structural elucidation of three of the four isomers (both photoproducts and one thermal product) was successful (compound **6-T** is the **t**entatively assigned structure). Taken together, the four isomers account for 70% conversion of starting material (**7**: **6-T** ca. 1.7:1 after complete thermal isomerization of **4** and **5**).

Comprehensive ^{1}H and ^{13}C NMR studies[5] were performed on photoproducts **4** and **5**. Both reveal a conversion from the acyclic homoenediyne moiety into a dihydrocyclopent[*a*]indene ring system spiro-fused to the 9-position of a 9,10-dihydroanthracene moiety.[6] X-ray quality crystals of compound **7** were obtained by isomerization of compound **5** in refluxing toluene for 3 h. The resulting X-ray structure of compound **7** is given in Figure 1. As shown, isomerization of **5** converts the 1,4-cyclohexadiene moiety to its corresponding phenyl moiety by selectively cleaving one of two possible carbon−carbon bonds. This isomerization also involves a transfer of hydrogen from the cyclohexadiene moiety to the dihydroanthracene moiety. Unfortunately, the structure of the thermal isomerization product of compound **4** could not be unequivocally confirmed by NMR, but very likely corresponds to the tentatively assigned isomer, **6-T** (Figure 1). Mechanistcally, a diradical pathway is suggested based on the $\mathbf{1}\cdot H^+{+}2H$ product observed from reaction in neat 1,4-CHD (reaction mixture "**a**"), as well as the observation of 1,4-addition of benzene to **1** (reaction mixture "**b**"). It should be noted that compound **1** is thermally unreactive well beyond the 18 °C temperature of the photochemical reaction. Specifically, ^{1}H NMR experiments monitoring compound **1** in toluene-d_8 at 100 °C for 18 h confirmed thermal stability within this temperature window.

The mechanism was probed by density functional theory (DFT) computations on the transformation of **1** (Figure 2). This study details the pathway to the experimentally seen intermediate **4** leading to the formation of the predicted product **6-T**. As the systems under consideration are large and open-shell, the experimental systems were reduced (anthracenyl was replaced by phenyl, *n*-butyl groups by hydrogens) to keep the key features and dominant electronic interactions; the model structures are named accordingly with a prefix "M", e.g., computed **M1** refers to the experimental structure **1**. The BLYP (Beck−Lee−Yang−Parr) combination of gradient-corrected exchange and nonlocal correlation functionals,[7] as implemented in the Gaussian03 program package,[8] was utilized for all computations. An unrestricted approach (UBLYP) with a 6-31G* basis set was used for the open-shell triplet states of the reactants, products, and diradical intermediates to model the photochemical nature of the title transformation. Even though the involvement of open-shell singlet states cannot be excluded, the assumption that the triplet and open-shell singlet potential energy surfaces (PES) are qualitatively similar is not unjustified. Computations of the open-shell singlet PES are currently not feasible and would most likely require an elaborate multireference treatment. Thermal and zero-point vibrational corrections of each

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[5] ^{1}H assignments were made using 2D gCOSY, TOCSY, and gNOESY experiments whereas ^{13}C assignments were made using 2D gHSQC-DEPT, gHMBC and selective gHMBC experiments. See the Supporting Information.

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[7] (a) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098−3100. (b) Lee, C. T.; Yang, W. T.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789.

[8] Gaussian 03: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision B.01; Gaussian, Inc.: Pittsburgh, PA, 2003.

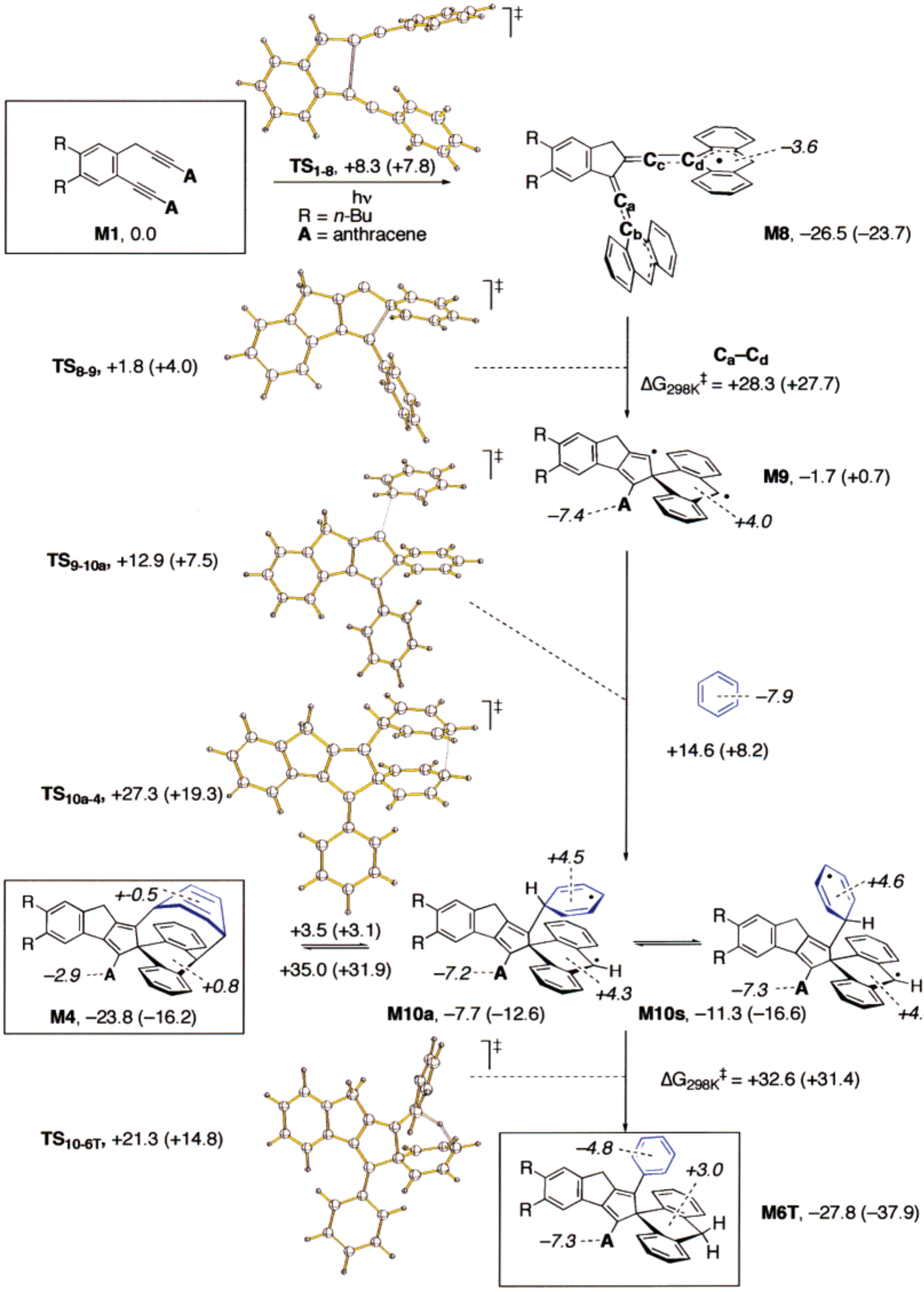

FIGURE 2. Proposed reaction cascade for the photochemical cyclization (modeled by the triplet state of all species) of **1** (modeled with **M1**); relative energies ΔG_{298K} (BLYP/6-31G*) and ΔH_0 (in parentheses at BLYP/6-311+G* + ZPVE(BLYP/6-31G*)); NICS values for the ring centers in italics.

species were obtained through calculation of the harmonic analytic vibrational frequencies. Energy single points and NICS (nucleus-independent chemical shifts at the ring centers as a measure of aromaticity;[6e,9] triplet states can be computed as well;[10] negative NICS indicate aromaticity) were computed with a larger triple-ζ (6-311+G*) basis set. All comparisons refer to ΔG_{298K} (BLYP/6-31G*) values, unless noted otherwise. We present in this discussion the transformation of **1** to **4** and **6-T**; the pathway from **5** to **7** was computed as well but is quite similar in all aspects so that it will not be discussed here.

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(10) Gogonea, V.; Schleyer, P. V.; Schreiner, P. R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1945.

The ring closure of the triplet starting material **M1** is accompanied by a low barrier for $\mathbf{TS}_{1-8}$ of only 8.3 kcal mol^{-1}, exothermically (-26.5 kcal mol^{-1}) resulting in the intermediate triplet diradical **M8**, which is highly stabilized through aromatic conjugation (note that the indicated NICS values are negative). The reaction proceeds through a high-lying ($+28.3$ kcal mol^{-1}) transition structure ($\mathbf{TS}_{8-9}$) to the shallow minimum **M9** that is just -1.7 kcal mol^{-1} below **M1**. The high energy required for this second cyclization is not surprising as one of the allenyl−benzyl-conjugated subunits present in **M8** is lost in **M9**; this is also evident from the $+4.0$ NICS value for the central ring. As a consequence, even the normally highly unfavorable addition of a benzene molecule (used as solvent) to **M9** is not very taxing because of spin delocalization in the intermediate biradical **M10** (**a**, *anti* and **s**, *syn*, 3.6 kcal mol^{-1} more stable). This stabilization is lost upon cyclization (through $\mathbf{TS}_{10a-4}$, $+35.0$ kcal mol^{-1}) of **M10a** to the observed **M4** ($+23.8$ kcal mol^{-1}). Equilibrium isomer **M10s** can react further through the hydrogen-shift $\mathbf{TS}_{10-6T}$ ($+32.6$ kcal mol^{-1}). Hence, the thermodynamic stabilities of **M4** and **M6T** are comparable and support the tentative assignment of **6-T**.

In closing, the photochemical cyclization of homoenediyne **1** offers several notable features, including: (i) visible-light promoted polycyclization via a diradical cascade reaction, (ii) trapping of diradical **M9** with benzene (solvent-turned-reagent) at an aromatic “cost” of 8.4 NICS units (C_6H_6 to **M4**), and (iii) the continued attenuation of aromatic character as a key steering force determining the remaining course of the reaction (qualitatively identified by the reported NICS values in Figure 2).

Acknowledgment. M.J.M. acknowledges support from the University of California Cancer Coordinating Committee, the National Science Foundation (CHE-0138143), and Dupont (Young Professor Award). P.R.S. acknowledges support from the National Science Foundation (CHE-0209857). S.E. acknowledges the Department of Education for a GAANN Fellowship.

Supporting Information Available: Detailed experimental procedures for compounds synthesized in this study, NMR analysis, supplementary data supporting all theoretical calculations, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0485132