Communication

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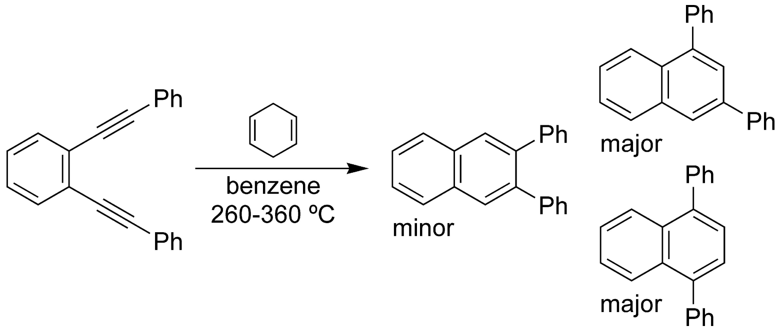
J. Am. Chem. Soc., **2005**, 127 (28), 9968-9969• DOI: 10.1021/ja042703c • Publication Date (Web): 25 June 2005



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Bergman Cyclization of Sterically Hindered Substrates and Observation of Phenyl-Shifted Products

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The Bergman cyclization,[1] a remarkable isomerization in which an enediyne (prototypical examples being **1** and **2** in Figure 1) forms an arene 1,4-diradical, has found applications in areas ranging from drug design[2] to materials synthesis.[3,4] Considerable effort has been expended to tune the reactivity of enediynes, primarily to decrease their barrier to cyclization,[5] an important consideration for designing viable therapeutic agents. By far the most common approach for reducing the energy of the transition state is to make cyclically constrained systems[6,7] such as enediyne **3** (E_a = 23.8 kcal/mol),[6] and this approach is well-represented in nature.[8] More recently, metal coordination[9] (**4**) and appropriate ortho substitution[10] (**5**) have been demonstrated as promising approaches for facilitating Bergman cyclizations under relatively mild conditions.

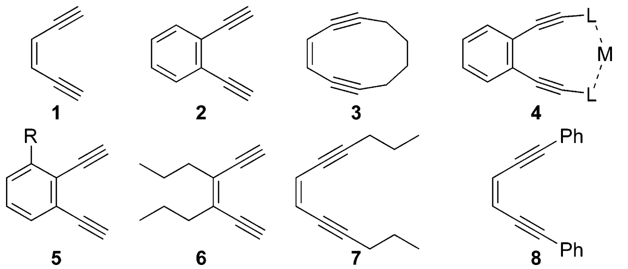


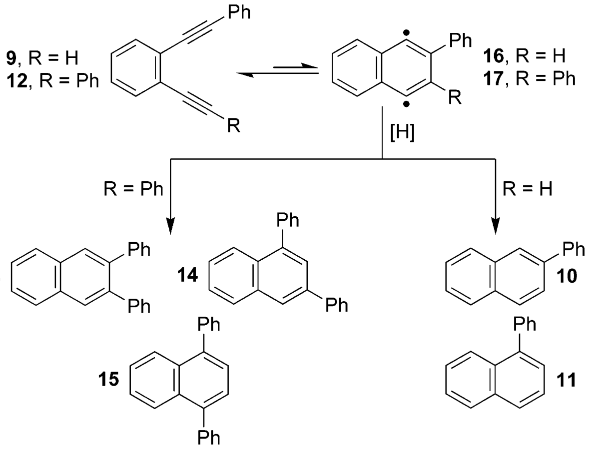
Figure 1. Examples of enediynes that undergo the Bergman cyclization.

Fewer studies have been carried out on derivatives with increased cyclization barriers, likely due to the large activation energy required for even unconstrained enediynes such as **6** (E_a = 27.4 kcal/mol).[11] For instance, the presence of the two propyl groups on enediyne **7** substantially increases the temperature required for cyclization relative to **6**.[11] One of the most hindered systems studied to date, (*Z*)-1,6-diphenylhex-3-ene-1,5-diyne (**8**), reacts at 280 °C.[12,13] In sterically demanding systems, theoretical calculations[14] indicate that the difference in energy between five- and six-membered ring formation is substantially reduced, and related modes of reactivity have been reported experimentally under photoinduced electron-transfer conditions[15] and upon reduction with lithium.[16]

Surprisingly, we have found that certain enediynes give rise to products that, while likely derived from an initially formed 1,4-didehydroarene, are not a simple result of cycloaromatization but rather involve one or more phenyl shifts. For example, the cyclization of 1-ethynyl-2-(phenylethynyl)benzene (**9**) (Scheme 1) produces the expected 2-phenylnaphthalene (**10**) upon thermolysis in benzene, with 1,4-cyclohexadiene (CHD) as the radical trapping agent, in 26−51% yield (for detailed procedures and yields of products under different reaction conditions, see Supporting Information). However, in addition to adducts[17] with the solvent and trapping agent, 1-phenylnaphthalene (**11**), which results from a phenyl shift, is observed in 2−5% yield. Similarly, the cyclization of **8** produced *o*-terphenyl in 17−28% yield in addition to *m*- and *p*-terphenyl, each in up to 4% yield.

More dramatically, the reaction of 1,2-bis(phenylethynyl)benzene (**12**) (Scheme 1) produced the expected isomer, 2,3-diphenylnaphthalene (**13**), as only a minor product (<3% yield) under all conditions studied. The conversion to **13** generally increased with higher reaction temperature (260−360 °C) and concentration of trapping agent (0.1−1 M CHD). The predominant species formed were 1,3-diphenylnaphthalene (**14**) (16%; 260 °C, 36 h, 1.0 M CHD) and 1,4-diphenylnaphthalene (**15**) (11%; 360 °C, 3 h, 1.0 M CHD), resulting from single and double phenyl shifts, respectively. Typically, these conditions also led to products in which one or more triple bonds had been hydrogenated in <5% yield. As is commonly observed in diradical chemistry, the formation of polymers contributes to a lower mass balance of cyclized products.[1] In this context it is interesting to note that photocyclization of **12** is reported to yield exclusively **13**.[18] Reactions of **12** in EtOH and *i*-PrOH also led to formation of the three isomeric diphenylnaphthalenes, albeit in lower yield due to the poorer H-donating ability of the alcohol solvents (see Supporting Information). Conducting the experiments in the presence of **13** led to no increased yield of **14** or **15**, thereby demonstrating that interconversion between diphenylnaphthalene isomers does not take place under these conditions. Remarkably, benzofulvenes[14] 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,[14] the majority of these products likely arise by radical attack[4,19] processes, as evidenced by the higher yields realized at lower reaction temperatures in combination with higher CHD concentrations.

Scheme 1. Reaction of Mono- and Diphenyl-Substituted Diethynylbenzene and Observed Phenyl-Shifted Products



The observation of a phenyl shift onto an sp^2 radical is without precedent in solution, although it has recently been proposed to explain some of the label scrambling detected in the flash vacuum pyrolysis of 3-phenylphthalic anhydride.[20] To assess the feasibility

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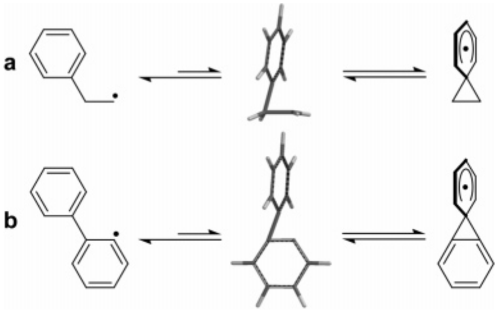
Scheme 2. Model Systems, Transitions States, and Intermediates Used for Computing the Energy Barrier Associated with Phenyl Shifting onto sp^3 (a) and sp^2 (b) Radical Centers (BLYP/6-31G*)



of such a transformation, calculations to determine the enthalpic barrier for the facile process of a phenyl ring shifting onto an sp^3 radical were carried out to allow comparison to the corresponding shift onto an sp^2 center. The barrier to formation of the spirocyclic transition state for 2-phenylethyl radical is 14.5 kcal/mol[21] (Scheme 2a). In comparison, the barrier for the corresponding transition state in the biphenyl radical is 42.9 kcal/mol (Scheme 2b) (see Supporting Information), signaling a dramatically greater barrier for phenyl shifting onto the sp^2 radical.

The high inherent barrier for phenyl shifting in an aryl system would be substantially lowered in cases where the isomerization is thermodynamically favored. For example, the initial species formed, 2,3-diphenylnaphthalene-1,4-diyl (**17**), in the cyclization of **12** experiences strong steric repulsion between adjacent phenyl rings. To quantify this, an isodesmotic computation on the transformation of **17** and *p*-naphthyne to 2-phenylnaphthalene-1,4-diyl (**16**) was carried out to derive an energy of interaction between the phenyl rings of 6.3 kcal/mol. Another driving force is the formation of more energetically stable diradicals. Experimental determinations[22] of the enthalpic heats of formation for isomeric benzynes indicate that the meta and ortho isomers are more stable than *p*-benzyne by 15.3 and 30.7 kcal/mol, respectively. Similarly, theoretical studies[23] predict the enthalpies of formation of 1,3- and 2,3-naphthyne to be lower than that of 1,4-naphthyne by 16.0 and 30.3 kcal/mol, respectively. The formation of more stable benzynes provides an additional driving force for the formation of phenyl-shifted products. Although relief of steric hindrance and formation of more energetically favorable benzynes will lead to a lowering of the barrier, it is not clear that these pathways are sufficiently low in energy[24] to explain the observed products, prompting exploration of two other pathways that could account for phenyl-shifted products. Isomerization of a triple bond to a vinylidene carbene, followed by cyclization, could be invoked to explain the occurrence of **14** in the thermolysis of **12**. However, heating (280 °C, 7 d, benzene) a model compound, 1-methyl-2-(phenylethynyl)benzene, did not result in formation of the expected phenylindenes,[25] thereby excluding vinylidene carbenes from potentially accounting for the phenyl-shifted products. Alternatively, a multistep mechanism for "phenyl walking" has been proposed for some isomerizations under flash vacuum pyrolysis conditions.[26] However, studies on a derivative of **12** in which the phenyl rings were perdeuterated confirmed that no deuterium transfer to the naphthalene ring occurred, thus ruling out this phenyl shifting mechanism (see Supporting Information).

In conclusion, the study of particularly hindered Bergman cyclizations revealed that phenyl shifts can dominate the products formed under certain conditions. This finding has an immediate impact on the structures expected for polymers produced utilizing phenyl-terminated enediyne monomers.[27] These findings are also relevant in formulating mechanisms for processes involving sp^2 radicals and phenyl rings, such as combustion chemistry and soot formation.[28]

Acknowledgment. The authors thank the ACS-PRF, the Oak Ridge Associated Universities (Ralph E. Powe Award), and the University of Michigan for funding.

Supporting Information Available: Synthetic procedures, tables containing yields, and coordinate files and methodology for computations. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA042703C