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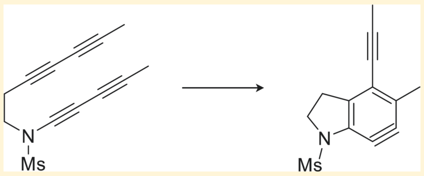
Mechanism and Regioselectivity of an Unsymmetrical Hexadehydro-Diels−Alder (HDDA) Reaction

Maggie Chen, Cyndi Qixin He, and K. N. Houk*

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569, United States

Supporting Information

ABSTRACT: Hoye reported intramolecular hexadehydro-Diels−Alder (HDDA) reactions to generate arynes that functionalize natural product phenols and amines. In their studies, Hoye found that unsymmetrical tetraynes selectively form a single aryne. We report density functional theory (DFT) calculations that reveal the factors controlling the regioselectivity.



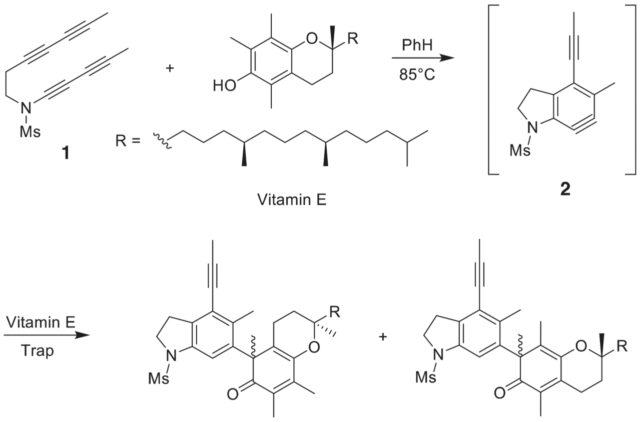
INTRODUCTION

The cycloaddition of an alkyne to a diyne to form a benzyne was first discovered by the groups of Johnson and Ueda independently in 1997.[1,2] This reaction was studied extensively and named the hexadehydro-Diels−Alder (HDDA) reaction in 2012 by Hoye and co-workers.[3] They established the intermediacy of benzynes and demonstrated the versatility of HDDA reactions. Through computational studies, our group showed that the regioselectivity of nucleophilic additions to arynes is determined by the distortion energies in the transition state. The benzyne carbon with a larger angle is more electrophilic due to smaller aryne distortion to achieve the transition state.[4,5] Here we explore the regioselectivity that occurs earlier along the reaction path and determine which intermediate aryne is formed by the HDDA. Recently, Hoye has shown that HDDA cascades can be used to synthesize functionalized polycyclic aromatics via benzynes.[6−15]

Our interest in this field was most recently aroused by Hoye and co-workers, who reported that many different natural products could be functionalized by arynes generated by HDDA.[16,17] The studies demonstrated that despite their high reactivities, benzyne intermediates are able to chemoselectively react with natural products. Scheme 1 demonstrates one of the experiments involving Vitamin E trapping. Tetrayne **1** undergoes intramolecular HDDA reaction to form benzyne intermediate **2**. The unsymmetrical benzyne then adds to the ortho positions of Vitamin E to form the ene products at 82% yield. Comparable yields were noted in cases where other natural products such as estradiol, sinomenine, tropinone, and limonene were used.

A common motif found in those trapping reactions involves the regioselective intramolecular HDDA of the unsymmetrical tetrayne **1** into benzyne **2**. While only products from a single benzyne were observed experimentally, there are four possible benzynes that could have been produced by HDDA reaction of **1** (Figure 1). The potential of forming a cyclobutadiene via bonds 1−1′ and 2−2′ is not likely due to high product instability (Figure S1), although Hoye et al. postulated benzyne cyclobutadienes in a different HDDA study.[18]

Scheme 1. HDDA Cascade with Vitamin E Trapping



We were intrigued by the origins of this selectivity and report here a computational study on the HDDA reaction of **1**.

COMPUTATIONAL METHODS

Calculations were performed with Gaussian 16[19] on structures optimized at the (U)M06-2X/6-311+G(d,p) level of density functional theory (DFT).[20,21] A model intramolecular HDDA reaction was used to benchmark (U)M06-2X/6-311+G(d,p) with other methods including (U)B3LYP/6-311+G(d,p) and (U)ωB97XD/6-311+G(d,p) (Figure S2 and Table S1). All three levels of theory predict the same stepwise mechanism.

RESULTS AND DISCUSSION

Previous studies have shown that HDDA reactions occur through a stepwise mechanism via diradical intermediates.[22−26] We first investigated the intermediates leading to each of the four possible products (Figure 2). Formation of benzynes **2** and **3** both involve intermediate **6**. Intermediate **7** leads to benzyne **4**, and **8** leads to benzyne **5**. Since **7** and **8** are less stable than **6** by 35.9 and 41.7 kcal/mol, respectively, we did not consider

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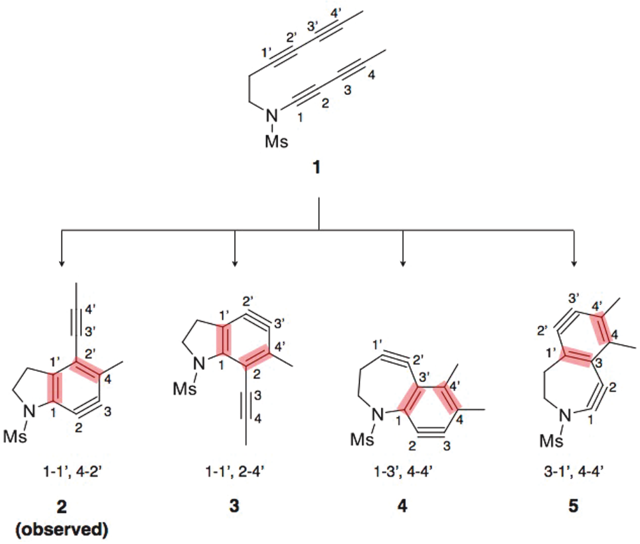

Figure 1. Possible products from the intramolecular HDDA of an unsymmetrical tetrayne. Bonds formed in the reaction are highlighted in red.

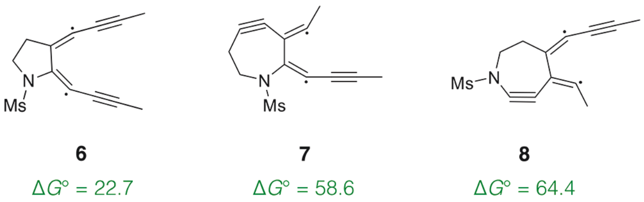

Figure 2. Intermediates formed in the first step of the stepwise HDDA reaction. Structures are optimized at the (U)M06-2X/6-311+G(d,p) level of theory. All energies are in kcal/mol.

them further, and there is no evidence that benzynes **4** and **5** are formed. The much lower free energy of **6** than **7** and **8** is due to both (1) the additional propynyl stabilization in **6**[27,28] and (2) the large triple-bond strain present in the aza-cycloheptynes, **7** and **8**.

To evaluate the effect of having one propynyl group stabilize the vinyl radical center vs conjugating to the vinyl π system, we compared two bimolecular HDDA reactions illustrated in Figure 3. Figure 3a mimics the double propynyl stabilization of intermediate **6**, while Figure 3b simulates the propynyl−vinyl conjugation in intermediates **7** and **8**. Propynyl group stabilization of the radical decreases the free energy by 12.6 kcal/mol. The same energy difference should apply to intermediates **6**, **7**, and **8** in the original intramolecular HDDA reaction, partially accounting for the relative instability of **7** and **8** compared to **6**.

Moreover, **7** and **8** both contain strained aza-cycloheptynes.[29] We evaluated the strain of aza-cycloheptynes in Figure 4, where **7′** and **8′** are truncated fragments of **7** and **8**, respectively, preserving the highlighted alkyne angles. Alkyne bending accounts for about 35 kcal/mol higher electronic energy in **7** or **8** than in **6**.

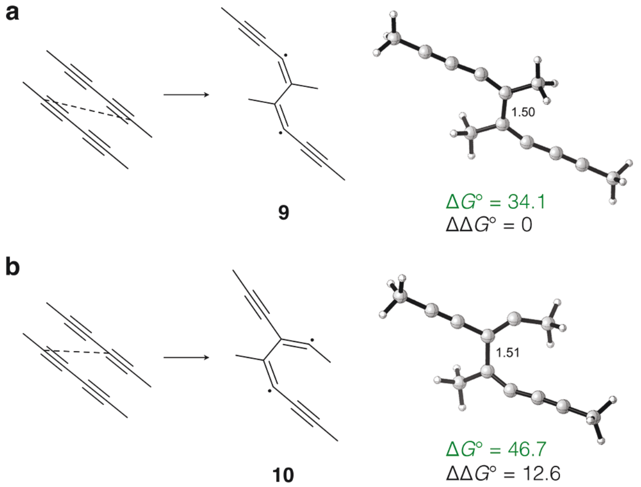

Figure 3. Model bimolecular HDDA reactions and the effect of propynyl stabilization. Structures are optimized at the (U)M06-2X/6-311+G(d,p) level of theory. All energies are in kcal/mol and distances in Angstroms.

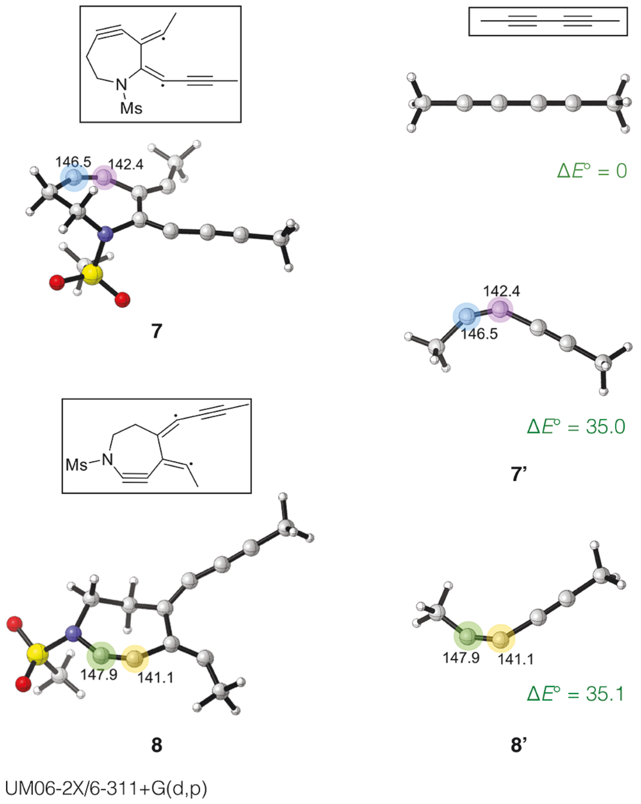

Figure 4. Triple-bond strain in model dimethylbutadiynes. Structures are optimized at the (U)M06-2X/6-311+G(d,p) level of theory. All energies are in kcal/mol. All angles are in degrees.

Of greater subtlety is what differentiates formation of **2** and **3**. Both could be formed via diradical intermediate **6**, as shown in Figure 5, with the corresponding (U)M06-2X/6-311+G(d,p) optimized structures illustrated in Figure 6. The transition structures for the concerted mechanisms were included as reference. Calculated energy barriers agree with previous literature and provide additional support for stepwise mechanism over concerted. In both pathways leading to **2** and **3** via the stepwise mechanism, the first step is rate-determining.

The activation barrier of the second step to form **2** is 4.3 kcal/mol. To form product **3**, the barrier is 6.6 kcal/mol (Figure 5). Benzyne angles in **2** and **3** are labeled in Figure 6. The carbons with larger angles are the sites of nucleophilic attack on the benzynes (e.g., Scheme 1) as described in our previous work.[4,5,7]

The difference in energy barrier is related to the difference in product stability: **3** is less stable than **2** by 3.4 kcal/mol.

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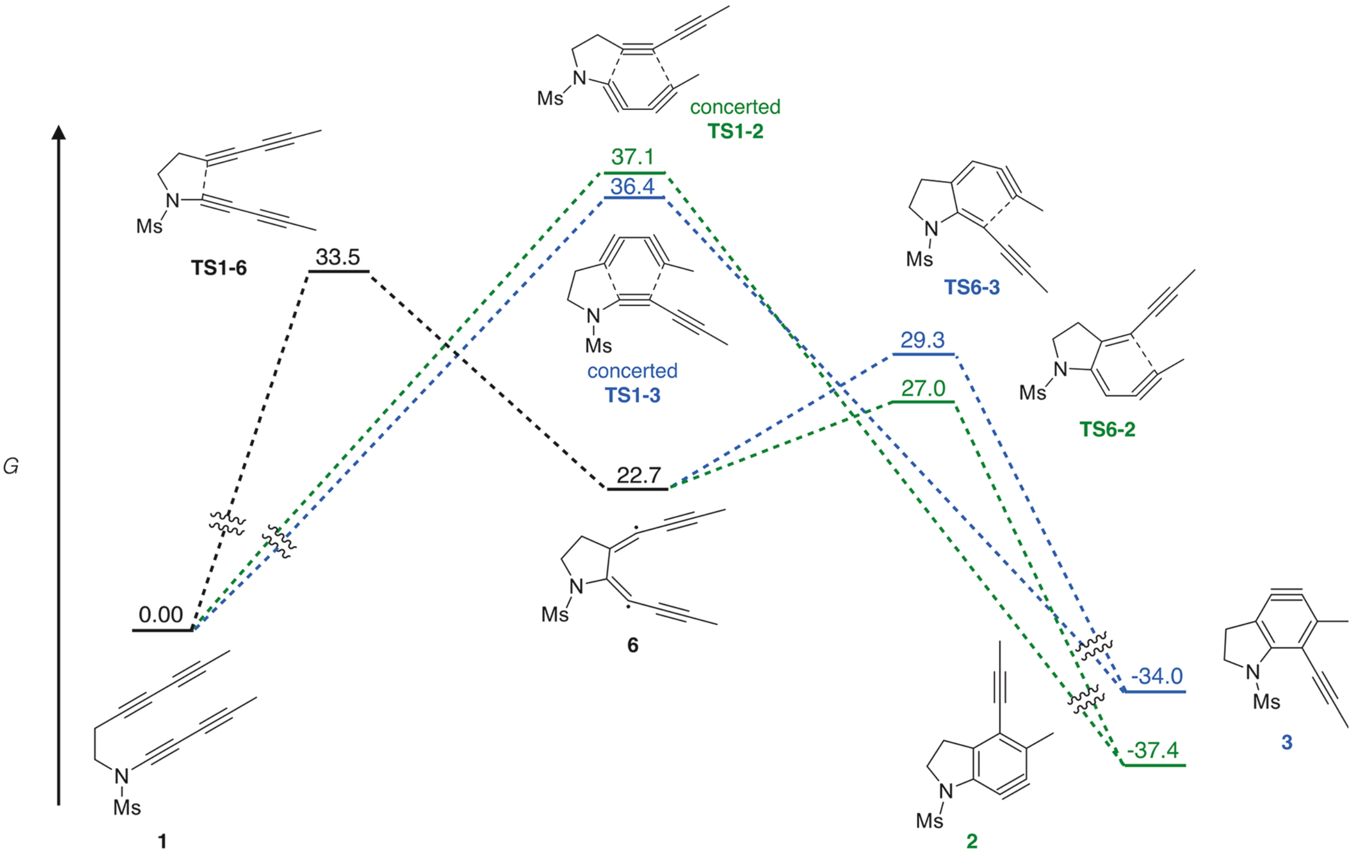

Figure 5. Concerted and stepwise mechanisms of HDDA reactions forming product **2** (observed) and product **3** in one free energy diagram. Energies are calculated at the (U)M06-2X/6-311+G(d,p) level of theory and are reported in kcal/mol.

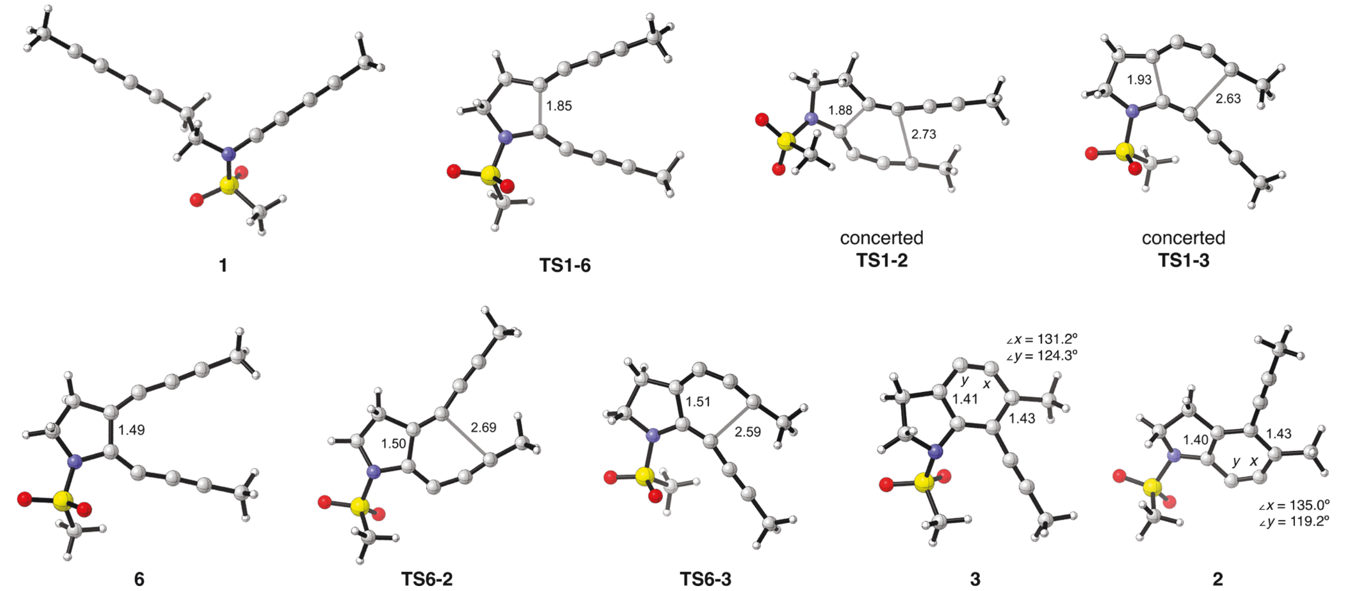

Figure 6. Optimized reactant, intermediate, transition state, and product structures for the concerted and stepwise mechanisms of HDDA reactions forming products **2** and **3**. Structures are optimized at the (U)M06-2X/6-311+G(d,p) level of theory. All distances are in Angstroms. Benzyne angles are included for the product structures.

Replacement of the mesyl group with a hydrogen leads to a negligible difference in free energy (0.2 kcal/mol). Similarly, in Figure 7c, the propynyl groups were also removed for reference, and the resulting products differ by only 1.0 kcal/mol. These model calculations indicate that **2** has less steric hindrance than **3** between the mesyl and the propynyl groups, accounting for the 3.4 kcal/mol difference in energy.

■ CONCLUSIONS

The rate-determining step of the HDDA reaction of tetrayne **1** leads to benzyne **2** among four possible products via a stepwise

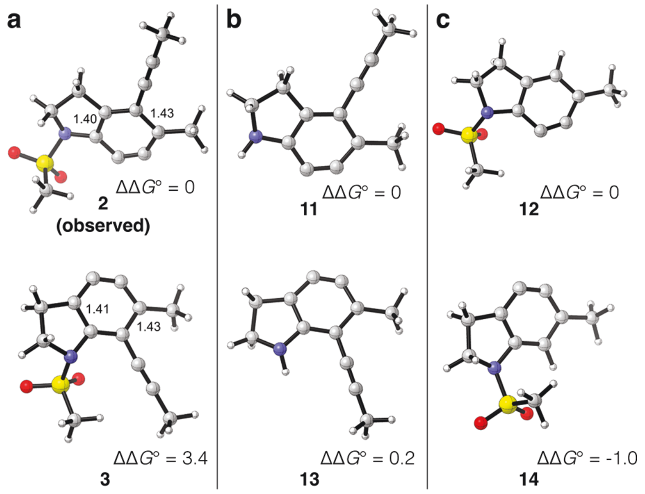

Figure 7. Model calculation to estimate steric interactions between the mesyl and the propynyl groups. Structures are optimized at the (U)M06-2X/6-311+G(d,p) level of theory. All energies are in kcal/mol; distances are in Angstroms.

mechanism. The intermediate **6** is much more stable than strained cycloheptyne alternatives, due to less ring strain and greater propynyl stabilization. The second step proceeds via the sterically less crowded transition state geometry.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b02865.

> Computational methods used; energetics of cyclobutadiene formation from **1**; comparison of 3 functionals for reaction of a model triyne; Cartesian coordinates of all computed species; references to methods and programs (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*houk@chem.ucla.edu

ORCID

K. N. Houk: 0000-0002-8387-5261

Notes

The authors declare no competing financial interest.

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