

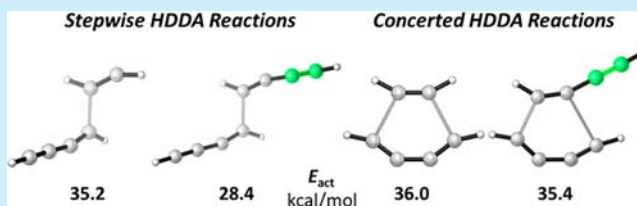
Why Alkynyl Substituents Dramatically Accelerate Hexadehydro-Diels–Alder (HDDA) Reactions: Stepwise Mechanisms of HDDA Cycloadditions

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S Supporting Information

ABSTRACT: The hexadehydro-Diels–Alder (HDDA) reactions between suitably substituted 1,3-diyne and alkynes produce highly reactive benzenes under thermal conditions without catalysts. DFT calculations and distortion/interaction analyses show that, for the activated substrates, the stepwise diradical pathway is more favorable than the concerted [4 + 2] process. One manifestation of this mechanism is that alkynyl substituents dramatically accelerate HDDA reactions, mainly by decreasing the distortion energy required to achieve the diradical transition state.

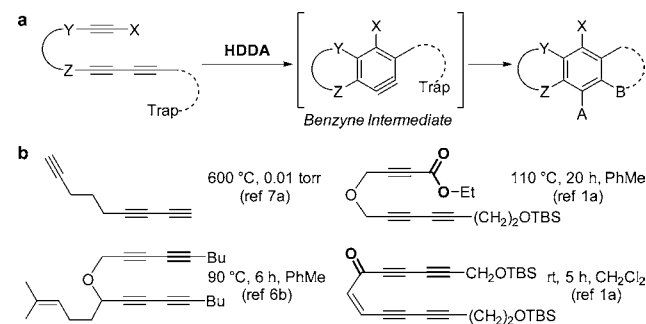


The cycloaddition between butadiyne and ethyne to generate benzyne is a highly unsaturated Diels–Alder variant and has been named the hexadehydro-Diels–Alder (HDDA) reaction.^{1a,2} The reverse process of this reaction is believed to play an important role in the combustion chemistry of aromatic compounds.³ According to *ab initio* computations, the concerted retro-HDDA route from benzyne to butadiyne and ethyne is consistent with the experimental observations.^{3a} However, it was also pointed out that the stepwise route through a singlet diradical intermediate may be competitive.^{3a} In 2011, Johnson et al. reported the (U)CCSD(T)//M05-2X computational results for the cycloaddition of butadiyne with ethyne.⁴ It was found that the concerted and stepwise routes to benzyne have very similar energetics, with only a 0.5 kcal/mol advantage for the concerted one.⁴

The power of the HDDA reaction in synthetic chemistry was greatly expanded through the recent discoveries by Hoye et al.¹ As shown in Scheme 1a, a 1,3-diyne undergoes the intramolecular [4 + 2] cycloaddition with an alkyne to produce a benzyne intermediate, which can be trapped *in situ* to give structurally complex benzenoid products in an atom- and step-economical fashion.⁵ Experimental explorations by the Hoye,¹ Lee,⁶ and other groups⁷ indicated that the substituents on the yne moiety affect the HDDA reactivities dramatically. Four representative HDDA substrates with their reaction conditions are given in Scheme 1b. The unactivated diyne-yne [4 + 2] cycloaddition was reported to occur under harsh conditions (600 °C, 0.01 Torr).^{7a} When the alkyne is activated by the ester group, the reaction temperature is decreased to 110 °C.^{1a} The use of an alkynyl substituted dienophile further lowers the temperature required for the HDDA reaction to 90 °C.^{6b} The combination of alkynyl and carbonyl activation enables the intramolecular reaction to occur even at room temperature.^{1a}

For normal electron-demand Diels–Alder (DA) reactions, the use of strong electron-withdrawing groups, such as the ester

Scheme 1. (a) Formation of Benzenes through HDDA Reactions and Subsequent Trapping Reactions To Generate Various Benzene Derivatives; (b) Representative Substrates and Conditions for HDDA Reactions



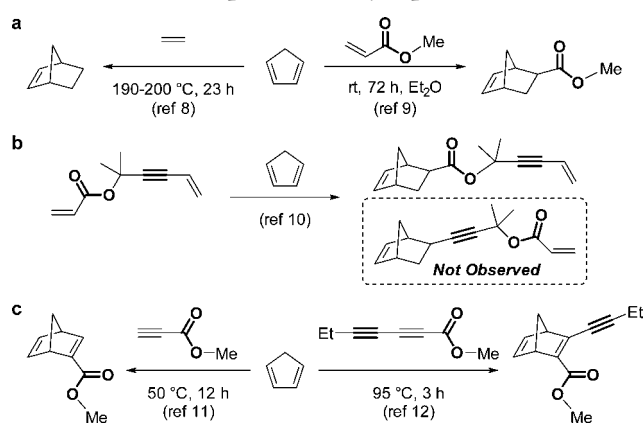
group, to activate the dienophile is a well-known strategy to lower the reaction temperature (Scheme 2a).^{8,9} The alkynyl group is much less effective than ester in the normal DA reaction of cyclopentadiene (Scheme 2b),¹⁰ and additional alkynyl substitution does not improve the DA reactivity of propiolate (Scheme 2c).^{11,12} These phenomena are significantly different from the observations in HDDA reactions (Scheme 1b).

To determine the mechanism and substituent effects of HDDA reactions, especially the origins of the unique activation by alkynyl groups, we have conducted a density functional theory (DFT) study of this intriguing process with the (U)M06-2X/6-311+G(d,p) level of theory.^{13,14} We showed earlier that this method gives relatively accurate energetics for cycloadditions.¹⁵

Figure 1 shows the transition structures TS1–4s for the formation of diradical intermediates from butadiyne and four

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Scheme 2. Effects of Ester and Alkynyl Groups on DA Reactivities of Dienophiles with Cyclopentadiene


dienophiles with different reactivities (ethyne, methyl propiolate, butadiyne, and methyl pentadiynoate). This step is rate-determining in the stepwise HDDA reactions (for details, see the Supporting Information). The transition structures **TS1–4-c** for the concerted reactions are also shown in Figure 1. The DA reactions of butadiene with ethene and cyclopentadiene with five dienophiles (ethene, methyl acrylate, butenyne, methyl propiolate, and methyl pentadiynoate) via transition states **TS5–10-c** were investigated for comparison (Figure 2).¹⁶ We also analyzed the activation barriers using the distortion/interaction model¹⁷ (or activation strain model¹⁸). In this model, the energy differences between the distorted transition structures and optimized ground-state structures are the distortion energies of the 2π component ($E_{\text{dist-}2\pi}$) and 4π component ($E_{\text{dist-}4\pi}$) in the DA reaction, respectively. The interaction energy (E_{int}) is the difference between the activation energy (E_{act}) and total distortion energy ($E_{\text{dist}} = E_{\text{dist-}2\pi} + E_{\text{dist-}4\pi}$).¹⁹ All of these results are summarized in Table 1.

The formation of benzyne from butadiyne and ethyne has activation energies of 35.2 and 36.0 kcal/mol for the stepwise and concerted reactions via transition states **TS1-s** and **TS1-c**, respectively (Table 1, entries 1–2). This suggests that the stepwise and concerted pathways are very competitive for the

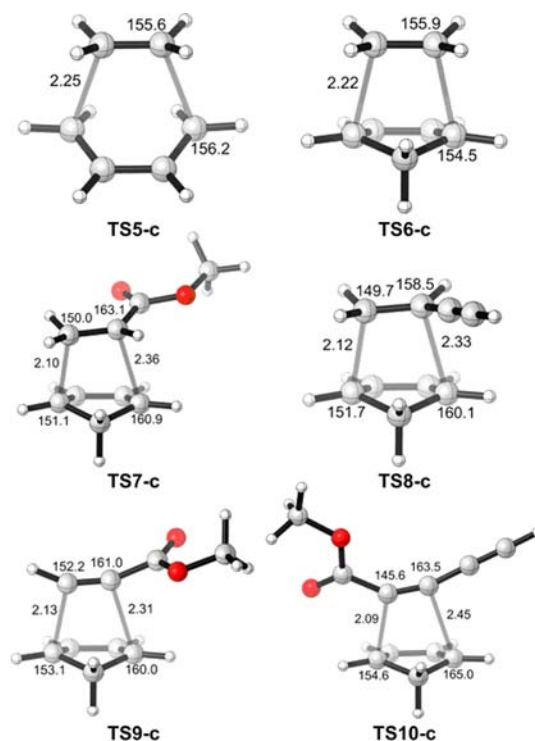


Figure 2. M06-2X/6-311+G(d,p)-optimized transition structures for the concerted DA reactions of butadiene with ethene and cyclopentadiene with dienophiles (distances in Å, angles or dihedral angles in deg).

unactivated diyne-yne [4 + 2] cycloaddition, in accordance with the conclusion from the (U)CCSD(T)//M05-2X computations.^{4,20} For comparison, the barrier for the generation of cyclohexene from butadiene and ethene via concerted transition state **TS5-c** is 19.6 kcal/mol (Table 1, entry 9), and the barrier for the stepwise diradical pathway is 35.4 kcal/mol.^{21,22} Interestingly, this reaction is 9.7 kcal/mol less exothermic than the HDDA reaction between butadiyne and ethyne (−47.6 vs −57.3 kcal/mol). Consequently, the much higher barrier for the HDDA reaction cannot be explained by the reaction exothermicity. As shown in Figure 1, a large deformation of

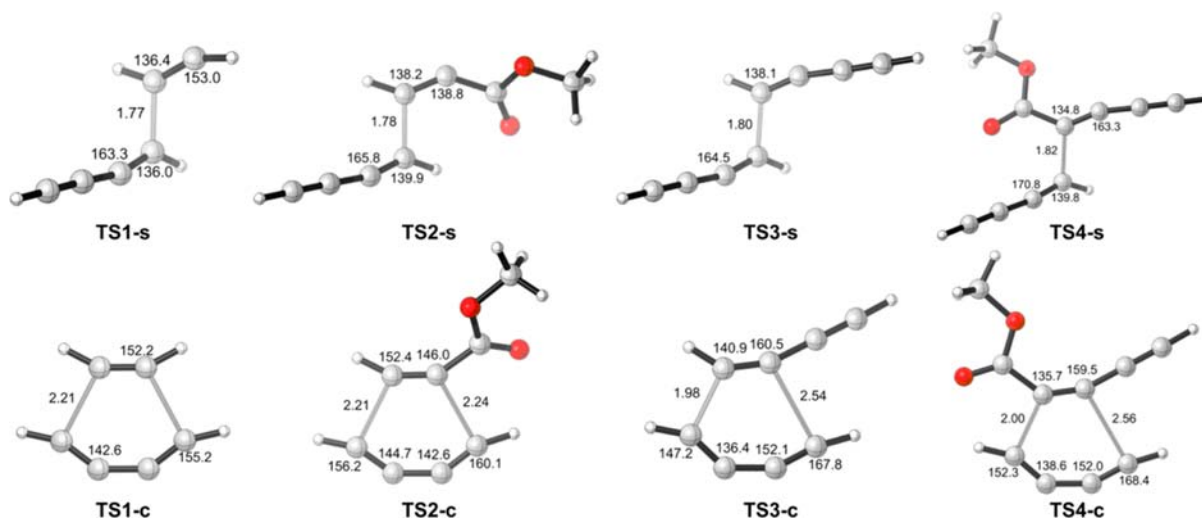


Figure 1. (U)M06-2X/6-311+G(d,p)-optimized transition structures for the stepwise and concerted HDDA reactions of butadiyne with dienophiles (distances in Å, angles in deg).

Table 1. (U)M06-2X/6-311+G(d,p)-Computed Activation, Distortion, and Interaction Energies (in kcal/mol)

entry	TS	E_{act}	$E_{\text{dist-}2\pi}$	$E_{\text{dist-}4\pi}$	E_{dist}	E_{int}
1	TS1-s	35.2	14.6	12.9	27.5	7.7
2	TS1-c	36.0	14.0	29.3	43.3	-7.3
3	TS2-s	28.8	18.8	10.7	29.5	-0.7
4	TS2-c	32.4	17.2	26.7	43.9	-11.5
5	TS3-s	28.4	11.6	11.6	23.2	5.2
6	TS3-c	35.4	16.1	27.9	44.0	-8.6
7	TS4-s	25.7	14.2	10.1	24.3	1.4
8	TS4-c	31.6	20.4	24.9	45.3	-13.7
9	TS5-c	19.6	7.3	18.7	26.0	-6.4
10	TS6-c	16.1	7.4	16.2	23.6	-7.5
11	TS7-c	10.1	8.1	15.2	23.3	-13.2
12	TS8-c	14.0	8.8	15.8	24.6	-10.6
13	TS9-c	14.0	10.5	15.2	25.7	-11.7
14	TS10-c	13.3	13.1	12.7	25.8	-12.5

the linear diyne is required to achieve the concerted HDDA transition state **TS1-c** ($E_{\text{dist-}4\pi}$ = 29.3 kcal/mol; Table 1, entry 2). The bend of two internal bond angles from 180° to 143° reduces the conjugative stabilization of diyne (9.3 ± 0.5 kcal/mol),²³ and more importantly, this results in repulsive orbital interactions between two distorted yne moieties. Therefore, the distortion energy of **TS1-c** is ~17 kcal/mol larger than that of the DA transition state **TS5-c** (43.3 vs 26.0 kcal/mol), while the interaction energies are almost identical (-7.3 and -6.4 kcal/mol; Table 1, entries 2 and 9). For the stepwise HDDA transition state **TS1-s** (Figure 1), the distortion energy is decreased by 15.8 kcal/mol (27.5 vs 43.3 kcal/mol; Table 1, entries 1–2) due to the much smaller geometrical change required for the diyne. However, the favorable interaction energy is also greatly reduced by 15.0 kcal/mol (7.7 vs -7.3 kcal/mol) because of the smaller orbital overlap between diyne and yne.

With activated diynophiles, the stepwise HDDA reactions are found to be more favorable, and the barriers are 3.6–7.0 kcal/mol lower than those for the concerted [4 + 2] process (Table 1, entries 3–8). Introducing an ester group on ethyne decreases the activation energy by 6.4 kcal/mol (28.8 vs 35.2 kcal/mol; Table 1, entries 1 and 3). This is consistent with the much lower temperature required in the experiment (Scheme 1b). The distortion/interaction analysis shows that the reduction in the barrier is due to the elimination of the repulsive interaction energy (-0.7 vs 7.7 kcal/mol). Such an interaction–acceleration effect also exists in the concerted DA reactions of cyclopentadiene with methyl acrylate and ethene: the methoxycarbonyl substituent increases the favorable interaction energy by 5.7 kcal/mol (Table 1, entries 10–11). These results indicate that the strong electronegativity of the ester group enhances the favorable interactions between the electron donor (diene or diyne) and acceptor (dienophile or diynophile) regardless of the mechanism (concerted or stepwise).

Experimentally, the alkynyl substituent improves the HDDA reactivity dramatically (Scheme 1b), and calculations reproduce this phenomenon. The stepwise HDDA reaction between two butadiynes has an activation barrier of 28.4 kcal/mol (Table 1, entry 5), 6.8 kcal/mol lower than that for the reaction between butadiyne and ethyne (35.2 kcal/mol; Table 1, entry 1). This suggests that the alkynyl substituent accelerates the HDDA reaction by ~5 orders of magnitude. The much higher reactivity of the diyne–diyne cycloaddition mainly comes from the lower distortion energy (23.2 vs 27.5 kcal/mol; Table 1, entries 1 and

5). Previous study showed that an ethynyl group stabilizes the methyl radical by 12.1 kcal/mol.²⁴ This is consistent with our calculations that the isodesmic reaction of butenyne with a vinyl radical to generate ethene and an ethynylvinyl radical is exothermic by 9.0 kcal/mol. Therefore, much less distortion is required for the diyne to reach its conformation in the diradical transition state **TS3-s** (Figure 1). Besides the distortion–acceleration effect, the alkynyl substituent, as a weak electron-withdrawing group, reduces the repulsive interaction energy by 2.5 kcal/mol (5.2 vs 7.7 kcal/mol; Table 1, entries 1 and 5).

For the reaction between butadiyne and methyl pentadiynoate, the activation energy via diradical transition state **TS4-s** is 25.7 kcal/mol, ~10 kcal/mol lower than that required for the unactivated HDDA reaction (Table 1, entries 1 and 7). This dramatic reduction in the barrier results from both the decrease of distortion energy and the reduction of the repulsive interaction energy, accounting for the very mild conditions for the intramolecular HDDA reaction with both alkynyl and carbonyl activation (Scheme 1b).

Notably, calculations show that the distortion–acceleration effect by the alkynyl group does not exist in the concerted HDDA reactions (Table 1, entries 2, 4, 6, and 8). The reactivities are controlled by the interaction energy. As the electronegativity of the alkynyl group is much smaller than that of ester, the reactivity of butadiyne is much lower than that of propiolate (35.4 vs 32.4 kcal/mol), and adding an alkynyl substituent slightly improves the reactivity of propiolate (31.6 vs 32.4 kcal/mol). This is inconsistent with the experimental results (Scheme 1b), showing that the concerted mechanism does not operate in the activated diyne–yne [4 + 2] cycloadditions. For the DA reactions of cyclopentadiene with dienophiles, no dramatic alkynyl activation is observed (Scheme 2b–c). This is in agreement with the computational results that there is no reduction in the distortion energy by alkynyl substituents in the concerted transition states (Table 1, entries 10 and 12–14). Therefore, the effects of the alkynyl substituent are closely related to the reaction pathway.

We have found that the HDDA reactions of the activated diynophiles occur through the stepwise diradical mechanism. This differs from the concerted mechanism favored by most conventional DA reactions. The alkynyl substituent accelerates the HDDA reaction by ~5 orders of magnitude mainly by decreasing the distortion energy required to achieve the diradical transition state.

■ ASSOCIATED CONTENT

📄 Supporting Information

Computational details and complete ref 13. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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†Y.L. and X.H. contributed equally.

Notes

The authors declare no competing financial interest.

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