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The Hexadehydro-Diels–Alder Cycloisomerization Reaction Proceeds by a Stepwise Mechanism

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Supporting Information

ABSTRACT: We report here experiments showing that the hexadehydro-Diels–Alder (HDDA) cycloisomerization reaction proceeds in a stepwise manner—i.e., via a diradical intermediate. Judicious use of substituent effects was decisive. We prepared (i) a series of triyne HDDA substrates that differed only in the R group present on the remote terminus of the diynophilic alkyne and (ii) an analogous series of dienophilic alkynes (n-$C_7H_{15}COC{\equiv}CR$) for use in classical Diels–Alder (DA) reactions (with 1,3-cyclopentadiene). The R groups were CF_3, CHO, COMe/Et, CO_2Me, $CONMe_2/Et_2$, H, and 1-propynyl. The relative rates of both the HDDA cyclization reactions and the simple DA cycloadditions were measured. The reactivity trends revealed a dramatic difference in the behaviors of the CF_3 (slowest HDDA and nearly fastest DA) and 1-propynyl (fastest HDDA and slowest DA) containing members of each series. These differences can be explained by invoking radical-stabilizing energies rather than electron-withdrawing effects as the dominating feature of the HDDA reaction.

The hexadehydro-Diels–Alder (HDDA) reaction is the most highly oxidized variant of the classic Diels–Alder [4 + 2] cycloaddition reaction.[1] In the latter, a 1,3-diene is engaged by a *dien*ophile; in the former, a 1,3-diyne is engaged by an alkynyl *diyn*ophile.[2] The latter typically results in cyclohexene formation, whereas the HDDA reaction leads to benzyne (or hexadehydrocyclohexene) formation (**1** to **2**; Figure 1a). A significant added dimension of the HDDA variant arises from the rich plethora of trapping reactions that make arynes highly versatile and valuable reactive intermediates. By comparison, all other members of the family of all-carbon Diels–Alder reactions engender new six-membered carbocycles that are at a stable oxidation state—cyclohexene, cyclohexadiene, or benzene depending upon whether zero, one, or two alkynes are present, collectively, in the 2π and conjugated 4π reaction partners.[3] We refer to the overall tandem process of HDDA cycloisomerization of a triyne followed by a benzyne trapping reaction as an HDDA cascade (**1** to **2** to **3**).[4] The initial HDDA cycloisomerization reaction is the rate-limiting event. The HDDA cascade is powerful for many reasons (e.g., it constitutes a synthetic strategy for de novo construction of benzenoid rings, allows facile access to benzynes of considerably more complicated structure compared with those from classical benzyne generation, can enable the discovery of new types of trapping reactions, and can serve as a platform for multicomponent processes[5]). As for any new reaction process and especially so for those with broad applicability, it is valuable to know the underlying mechanistic details that govern the reactivity.

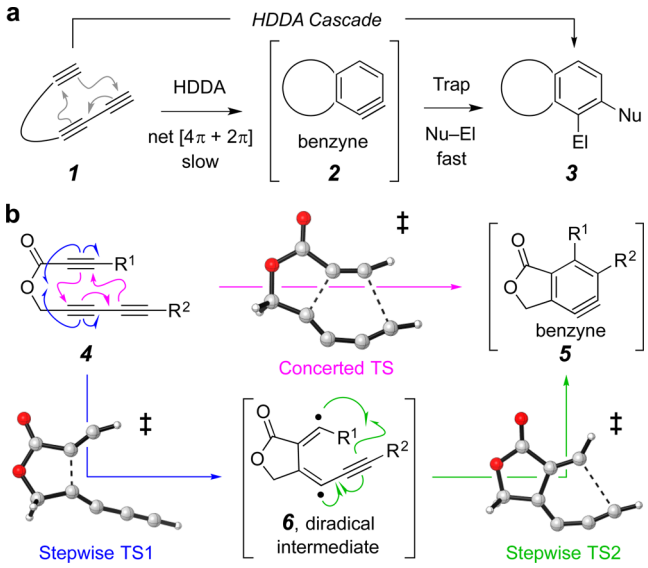

Figure 1. (a) The HDDA cascade: hexadehydro-Diels–Alder (HDDA) cyclization of triyne **1** to give benzyne intermediate **2** followed by rapid (intra- or intermolecular) trapping to yield **3**. (b) Concerted vs stepwise cycloisomerization pathways.

Computational [density functional theory (DFT)] studies have been used to explore aspects of the mechanism of the HDDA cycloisomerization reaction.[6] These encompass both (hypothetical) intermolecular and prototypical intramolecular examples. The calculations indicate that the activation energies for stepwise and concerted processes are similar, although a preference for a stepwise mechanism through a diradical intermediate[7] was often seen. We used[6e] the relative rates of cyclizations of a series of esters **4** to give, ultimately, phthalide lactones **5** (Figure 1b) to guide our choice of an optimal method[6f] to account for measured experimental reactivities. The transition state (TS) geometry for the concerted process for the specific case of ester **4** (R^1, R^2 = H; magenta) was 6 kcal mol^{-1} higher in energy than the TS leading from **4** to diradical **6**. The closure of **6** to **5** was nearly barrierless. In other words, this computation suggests that **6** is extremely short-lived, which,

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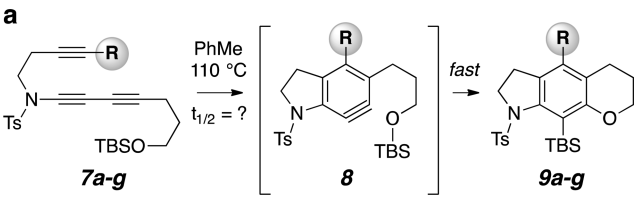
incidentally, is consistent with the fact that we have seen no consequences of radical character in any of the many modes of HDDA trapping reactions we have studied.

In the study reported here, we decided to systematically evaluate diynophile substituent effects on the rate of the HDDA reaction to see whether experimentation could distinguish between stepwise and concerted reaction pathways. Accordingly, we identified the series of triynes **7a**–**g** (Figure 2) as an



triyne	R	conditions (from 7a)
7a	H	—
7b	$CONEt_2$	1) *n*-BuLi, THF, CO_2 2) EDCI, Et_2NH, DMAP, DMF
7c	CO_2Me	*n*-BuLi, THF, $ClCO_2Me$
7d	COMe	*n*-BuLi, THF, Ac_2O
7e	CHO	1) *n*-BuLi, THF, $(CH_2O)_n$ 2) DMP, $NaHCO_3$, CH_2Cl_2
7f	C≡C–Me	1-bromoprop-1-yne, CuCl, NH_2OH•HCl, *n*-$BuNH_2$, CH_2Cl_2
7g	CF_3	$TMSCF_3$, CuI, K_2CO_3,TMEDA, DMF, air

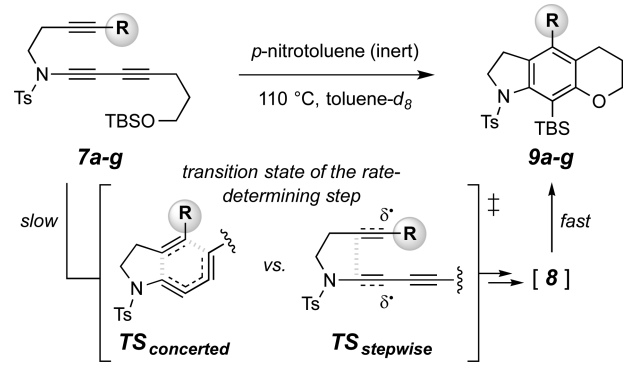
Figure 2. (a) HDDA cycloisomerization of triynes **7a**–**g** to form indoline derivatives **9a**–**g** via benzynes **8**. (b) Synthesis of **7a** and conditions for its conversion to **7b**–**g**.

appropriate group of compounds for measurements of their relative rates of HDDA cyclization. The choice of this set of substituents was guided by the prevalent use of many as activators of classical Diels–Alder reactions. The inclusion of the alkynyl substituent in tetrayne **7f** was based on the observation of Houk and co-workers that an alkynyl substituent on the terminus of the diynophile significantly lowered the activation barrier computed for the HDDA reaction for the intermolecular HDDA net cycloaddition reaction of 1,3-butadiyne with itself versus its reaction with ethyne.[6b]

Diynamide substrates like **7** are known to be well-behaved, cyclizing at convenient rates and giving rise to indoline products in good yields.[1,8] The products **9a**–**g** are formed via the HDDA cascade comprising initial, rate-limiting cycloisomerization of **7** to benzynes **8** followed by rapid trapping by the pendant silyl ether. In every instance, product **9** was by far the major product formed and, most often, the only product observed. The yields of **9a**–**g** following isolation were in the range of 42–82%.[9]

The relative rates of the HDDA cyclization were determined by ^{1}H NMR spectroscopic analysis of reactions performed in toluene-d_8 at 110 °C.[10] Integration of the growth of resonances from products **9** versus those of an inert internal standard (*p*-nitrotoluene) as a function of time allowed identification of the reaction half-lives. These are listed in Table 1.

Table 1. Relative HDDA Reaction Rates of Triynes 7a–g and Their Comparisons with Hammett Constant (σ_p) and Radical-Stabilizing Energy (RSE) Values



triyne	R	$t_{1/2}$[a]	k_{rel}	σ_p	RSE[b]
7f	**–C≡CMe**	0.26	320	0.03	**–12.1**
7e	–CHO	0.82	100	0.42	–7.7
7d	–COMe	5.1	16	0.34	–6.7
7c	$-CO_2Me$	9.2	9.1	0.34	–4.9
7b	$-CONEt_2$	84	1	0.26	–4.9
7a	–H	> 400	–[c]	0	0
7g	**$-CF_3$**	> 600	–[c]	0.54	**+1.9**

[a]Experimentally measured half-lives (in h). [b]Radical-stabilizing energy (in kcal mol^{-1}) of the substituent on a (C_{sp^3}-centered) radical. [c]The reactions were sufficiently slow at 110 °C for triynes **7a** and **7g** that 50% conversions were not achieved. At 145 °C, **7a** converted ca. 1.5 times faster than **7g**.

We first consider the reactivities within the set **7a**–**e**. These correlate reasonably well with the expected substituent effects (see below) in classical Diels–Alder dienophile activation (i.e., approximately CHO > COR > CO_2R > $CONR_2$ > H). This trend is also suggested by comparison to the Hammett σ_p values,[11] which reflect the electron-withdrawing character of the groups present in **7a**–**e**. It is tempting to be satisfied that this trend mirrors that of dienophile reactivity in classical Diels–Alder reactions.[12] However, values of a less often used parameter, the radical-stabilizing energy (RSE),[13] are also given in Table 1. These also are qualitatively in line with the reactivity trend observed for **7a**–**e**. We return below to consider the rates of the alkynyl- and trifluoromethyl-bearing triynes **7f** and **7g**.

How well do the relative HDDA reactivities for the specific set of reactants **7a**–**g** compare with dienophile substituent effects in classical Diels–Alder cycloadditions? We were surprised to find a relative paucity of data addressing, in a quantitative way, dienophilic reactivity in a set of analogues in which only a single substituent has been varied. In fact, we could find only two reports of such studies,[14] and neither encompassed the array of substituents we desired for comparison with the full set of analogues **7a**–**g**. Therefore, we prepared the series of electron-deficient alkynes **13a**–**g** (see

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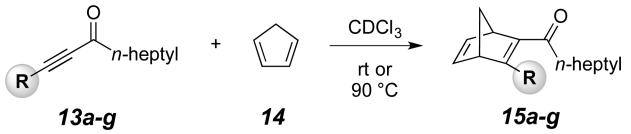
the Supporting Information). These again differ only in the substituents R, the natures of which correspond directly to those in triynes **7a–g**. Competition studies were used to determine, in pairwise fashion, the relative reactivities of these dienophiles. We used the classic approach of exposing a substantial excess of each of the two competing reactants, in this case 10 equiv each of two different dienophiles **13**, with the limiting reactant, here cyclopentadiene (**14**). Under the assumption that the reaction is essentially irreversible, the product ratio is a direct reflection of the relative rate constants for the two competing DA reactions because the initial concentrations of both dienophiles remain nearly constant throughout the course of the reaction.

The dienophiles are listed in Table 2 in order of decreasing reaction rate (red to blue). It should be noted that the reaction

Table 2. Relative Rates of Diels–Alder Cycloadditions of Alkynes 13a–g with Cyclopentadiene (14)



13a-g *14* *15a-g*

dienophile	R	k_{rel}[a]	σ_p	RSE
13e	–CHO	47,000	0.42	–7.7
13g	**–CF_3**	16,800	**0.54**	+1.9
13d	–COEt	2,100	0.34	–6.7
13c	–CO_2Me	840	0.34	–4.9
13b	–$CONMe_2$	50	0.26	–4.9
13a	–H	10	0	0
13f	**–C≡CMe**	1	**0.03**	–12.1

[a]Determined by ^{1}H NMR analysis of pairwise competition reactions using two dienophiles (10 equiv each) and cyclopentadiene in $CDCl_3$ in a sealed vessel (see the Supporting Information).

of the propynyl-substituted compound **13f** is the slowest of all[6b] and that the reaction of trifluoromethylated alkyne **13g** is one of the fastest. The Hammett σ_p and RSE parameters are also listed. The results are much better aligned with the electron-withdrawing nature of the substituent, as expressed by σ_p, rather than with its radical-stabilizing character, as reflected in the RSE values.

What have we learned from the HDDA reactivity of compounds **7f** and **7g** vis-à-vis the rates of Diels–Alder cycloaddition of ynones **13f** and **13g**? Indeed, it was the dichotomous nature of the electron-withdrawing effects (σ_p) versus the radical-stabilizing effects (RSE) of alkynyl versus CF_3 substituents (see Table 1) that led us to include tetrayne **7f** and trifluoromethylated triyne **7g** among the HDDA substrates we studied. The results are quite definitive. Tetrayne **7f**, whose alkynyl substituent has the largest RSE but only negligible electron-withdrawing power, reacts fastest, and trifluoromethylated alkyne **7g**, with its non-radical-stabilizing and strongly electron-withdrawing CF_3 substituent, reacts slowest (Table 1, red vs blue, respectively) of all the HDDA substrates we studied. This is clearly supportive of a stepwise mechanism for the HDDA cycloisomerization reaction, in which the substrate **16** proceeds via an initial (and rate-determining) closure to the diradical intermediate **18** via "stepwise TS1" rather than proceeding directly to benzyne **17** via the "concerted TS" (Figure 3). This conclusion is in accordance with earlier

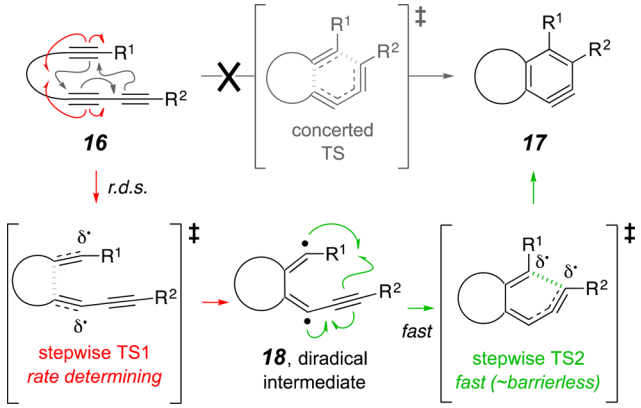


Figure 3. HDDA cycloisomerization (i.e., **16** to **17**) proceeds via diradical **18** rather than through a "concerted TS" geometry; the relative rate data indicate that "stepwise TS1" defines the rate of reaction.

computational analyses.[6b,c,e] Finally, it should be recalled that those studies also indicated that recombination within the diradical **18** to complete the formation of the carbocyclic benzyne occurs with an extremely low activation barrier. Circumstantial evidence supports this view; we have never observed a product from any HDDA cascade experiment that suggests that diradical **18** is of any practical consequence. All told, our experimental data validate the mechanistic pathway laid out in Figure 3 for the HDDA cycloisomerization.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b03786.

New compound preparation, spectroscopic characterization data, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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