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The Photochemical Hexadehydro-Diels-Alder ($h\nu$ -HDDA) Reaction

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Abstract

We demonstrate that the hexadehydro-Diels-Alder cycloisomerization reaction to produce reactive benzyne derivatives can be initiated photochemically. As with the thermal variant of the HDDA process, the reactive intermediates are formed in the absence of reagents or the resulting byproducts required for the generation of benzyne by traditional methods. This photo-HDDA (or $h\nu$ -HDDA) reaction occurs at much lower temperatures (including even at $-70\text{ }^{\circ}\text{C}$) than the thermal HDDA, but the benzyne produced behave in the same fashion with respect to their trapping reactions, suggesting that they are of the same electronic state.

Graphical Abstract

The thermal cycloisomerization reaction of substrates containing a 1,3-butadiene linked to a remote alkyne to generate a benzyne intermediate (**1** to **2**, Figure 1a),¹ has been shown to have remarkable generality.^{2,3} We have dubbed this cyclization process the hexadehydro-Diels-Alder (HDDA) reaction^{2a} because both the reactant pair and the carbocyclic product lack six of the hydrogen atoms that are present in the textbook prototype Diels-Alder [4+2] cycloaddition—the reaction between 1,3-butadiene and ethylene to give cyclohexene. The HDDA variant is additionally powerful because it produces benzyne derivatives, highly versatile organic reactive intermediates. The HDDA reaction has already been shown to be not only a valuable platform for the discovery of new trapping reactions of benzyne (e.g., **5**

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Experimental details for the preparation of all new compounds, as well as their spectral characterization data and copies of ^1H , ^{13}C , and ^{19}F NMR spectra (PDF).

Notes

The authors declare no competing financial interest.

to **6**,⁴ Figure 1b),^{3c} but an important construct for revealing fundamentally new mechanistic insights^{3,5} about aryne reactivity as well. These advantages largely stem from the fact that the HDDA reaction produces the benzyne derivative in a pristine environment that is free of the reagents and byproducts that, necessarily, accompany virtually every other traditional method⁶ of producing an aryne.

The energetics of the two stages of an HDDA cascade—i) rate-limiting benzyne generation and ii) subsequent (and rapid) in situ trapping—are notable. The initial cycloisomerization to the benzyne (e.g., **4** to **5**, Figure 1b) is exergonic by, typically, ca. 50 kcal•mol⁻¹.⁷ Subsequent trapping typically releases another ca. 80 kcal•mol⁻¹ of energy^{5f} as the highly strained benzyne⁸ proceeds to the final product(s). Indeed, alkynes bring a tremendous amount of potential energy to the reaction vessel!

The rate of the thermal HDDA cyclization of triyne substrates is highly dependent on the nature of the linker that joins the diyne and diynophile pair. Although a select few classes of linker atoms permit reactions to occur in a matter of hours at temperatures at or below ambient,⁹ it is much more common for the reactions to proceed with a half-life of several hours between, say, 70 and 150 °C and a few successful cyclizations have been observed even up to 200 °C.^{2a} We now report that certain types of poly-yne substrates can be smoothly cycloisomerized to benzynes upon ultraviolet (UV) irradiation at temperatures well below the thermal HDDA threshold (cf. **7a** to **8**, Figure 1c).¹⁰ The resulting benzyne (**9**) behaves in essentially identical fashion to that produced by the thermal process, indicating that the benzyne is born in the same electronic state whether its genesis lies in the thermal or photochemical HDDA variant. This is consistent with the mechanism of the reaction, which has recently been shown to be a stepwise event passing through a very short-lived diradical intermediate.^{7,11}

When a (Pyrex®) NMR sample tube containing a solution of **7a** in CDCl₃ was irradiated simultaneously with both 254 and 300 nm light sources (Rayonet reactor), the reaction progress was periodically monitored. This substrate contains *o*-methoxyphenyl substituents, which we hoped would lead to efficient intramolecular interception of the benzyne intermediate. As expected, the rate of consumption of the tetrayne was dependent, qualitatively, on the photon flux. The ¹H NMR spectrum of the reaction product mixture was very clean and product **8** could be isolated in 90% yield. We also observed resonances showing that methanol, dimethyl ether, 1,1,1-trichloroethane, and chloromethane were formed as byproducts in this photochemically induced reaction [as well as in its thermal counterpart (see below)]. These byproducts reveal the fate of the methyl group that is lost during the **7a** to **8** conversion. Upon intramolecular capture of the benzyne by the proximal *o*-methoxy substituent in **9**, the presumed zwitterion **10** is protonated/deuterated by adventitious water, methanol (produced in situ), or CDCl₃ and the resulting counterions HO⁻, MeO⁻, or Cl₃C⁻ then demethylate the oxonium ion **11**, giving rise to the observed array of byproducts. We also could effect this photon-induced transformation of **7a** to **8** at ca. -70 °C, where it again proceeded cleanly, demonstrating that this HDDA reaction can be effected at sub-ambient temperatures.

Comparison of the behavior of tetrayne **7a** under thermal conditions is instructive (Fig. 1c). Upon heating a CDCl₃ solution of this HDDA substrate in a 75 °C bath, we observed (¹H NMR monitoring) the half-life for its disappearance to be 12 hours. The dibenzofuran derivative **8** again was smoothly formed. On a preparative scale, it was isolated, following chromatographic purification, in 91% yield. Thus, the outcome of the thermal reaction was very similar to that of the photochemical. Moreover, photoinitiation was clearly responsible for the latter.

All of the reactions we describe in this report of the hν-HDDA reaction use tetrayne substrates that, like **7a**, bear arenes on the remote terminus of each 1,3-diyne. The additional substrates we have examined, **7b-l**, are shown in Figure 2a. The absorption spectra of selected members of this set are shown in Figure 2b. These aryl diynes show significant absorption in readily accessible regions of the UV spectrum. The absorption spectrum of the dialkylated analog **7i** (green) is included for comparison; clearly the conjugation provided by aryl substitution is advantageous, perhaps essential, for rendering the substrate photoreactive—indeed, **7i** has not proven to be a functional hν-HDDA substrate in our experiments, including irradiation at 254 nm.

Each of the tetraynes **7b-l** lacks the ortho-methoxy substituents present in **7a**; hence, it was necessary that these compounds be irradiated in the presence of an external trapping agent (cf. Nu/El, Fig. 1a) in order to capture the in situ-generated benzyne. An array of such reactions is shown in Figure 3 for the bis-*p*-carbomethoxy tetrayne **7b** (and Figure 4 for the other tetrayne substrates). Irradiation of **7b** produces **13** following capture of the hν-HDDA benzyne **12** (Figure 3a). Many types of trapping species are competent. Products **14–21** (Figure 3b) arise from reaction of **12** with π-type reagents. Capture by tetraphenylcyclopentadienone (1.5 equiv), leading to **14** (after loss of carbon monoxide, even at ambient temperature), was a very efficient process.¹² We used this reaction to more thoroughly explore the effect of various light sources and types of glass reaction vessel to promote the hν-HDDA reaction. Among the pairings of 254 vs. 300 nm source and quartz vs. Pyrex® reaction tubes, we settled on 300 nm through quartz as a convenient combination of speed vs. cleanliness of reaction.

Adducts **15–17** arise from trapping by 2,5-di(methoxymethyl)furan, *N*-benzoyl-2,5-dimethylpyrrole, and perylene (following spontaneous loss of dihydrogen¹³), respectively. Norbornene gives the benzocyclobutene derivative **18** in excellent yield. In a larger scale (0.5 g) reaction **18** was isolated in 75% yield. Anthracene traps to produce the triptycene derivative **19**. Diazo-acetate and -malonate esters and the derived indazole products **20** and **21**, respectively, are compatible with these photochemical conditions.

Nucleophilic traps (Figure 3c) to give adducts **22–25** work well. Although the benzyne **12** is unsymmetrical, the internal bond angles at carbons a and b are computed [DFT SMD(chloroform)/M062X/6–31+G(d,p)] to be nearly identical (126.6° vs. 128.9°). As such, the bias for attack by an external nucleophile¹⁴ should be governed more by steric rather than distortion factors. The products **22–24** were all formed as a mixture of constitutional isomers; the adduct having attachment of the nucleophile at carbon atom a (C_a) being favored in each case.¹⁵ Disulfide addition to give adduct **25** was also observed; several

mechanistic possibilities, both polar and radical in character, can be envisioned for this trapping reaction.¹⁶

We note that each of the diazo-derived adducts **20** and **21** was produced as a single regioisomer. nOe studies were insufficient in allowing for definitive assignment of the structure. The adducts are ascribed as shown based on the assumption that the steric bias in the transition state for the dipolar cycloaddition¹⁷ steers the bulky ester-bearing carbon atom of the diazo group away from the larger aryl substituent adjacent to C_b; the methylene carbon adjacent to C_a is retracted by virtue of residing in the fused five-membered ring and interferes less with approach of the dipole.

To establish additional aspects of the scope of this reaction, we studied the tetraynes **7d**¹⁸⁻⁷¹ (see Fig. 2a), which gave the products shown in Figure 4 (panels a and b for substrates containing malonate vs. non-malonate linker units, respectively). Substrates with either electron-donating or -withdrawing substituents on the arene ring are competent *hν*-HDDA benzyne precursors. Dihydrogen transfer (cf. **26**) was observed when **7d** was irradiated in the presence of cyclooctane.⁴ It is notable that the H₂-transfer occurs even under the mild, ambient temperature conditions of the *hν*-HDDA reaction. Curiously, trapping of the benzyne from **7e** with diisopropylamine in CDCl₃ gave the aniline derivative **27** with a predominantly deuterated arene hydrogen (86:14 = D:H). A control experiment showed no evidence for deuterium exchange of the *i*-Pr₂N-*H* with the CDCl₃ solvent, so we conclude that an initial 1,3-zwitterion from attack of the benzyne by the secondary amine gains its hydrogen atom by preferential abstraction of a deuteron directly from the carbon-acid CDCl₃. Acetic acid captures the photo-benzyne from **7f** efficiently (cf. **28**). Because the bis-diphenylamino-bearing tetrayne **7g** has a significantly red-shifted absorption maximum (Fig. 2b), we used 365 nm lamps as the light source to produce **29**. 1-Naphthalenyl substituents are well tolerated (cf. **30** and **31**). Formation of products **32–34** (Figure 4b) demonstrates that the buttressing effect afforded by the geminal dimethyl ester substituents in the malonate linked tetraynes (Figure 4a) is not essential. This is particularly noteworthy for the case of the “bare” trimethylene linker^{1a} in **7j**, the precursor to **33**. Product **32** is formed as a pair of diastereomers in a ratio of 2:1, regardless of whether the HDDA benzyne is generated thermally or photochemically, providing another indication that the reactive intermediates are on the same electronic state energy surface.

Finally, we examined the unsymmetrically substituted tetrayne **7c**, which bears one electron-donating and one -withdrawing group on each of its aryl substituents (Figure 5). This was activated either photochemically (ca. 22 °C) or thermally (90 °C) in the presence of cyclooctane to produce the reduced benzenoids **36** and **36'**. These arise from H₂-transfer to the constitutionally isomeric benzyne **35** and **35'**, respectively. We observed essentially the same ratio of products **36:36'** in each experiment, indicating that the same ratio of **35:35'** was formed under the two different modes of initiation. This, in turn, suggests that each of the diradical intermediates^{7,11} arising from initial bond formation (see red dashed line in **7c**) has the same electronic configuration and that each closes, competitively, with the same energetics to produce the same 2:1 ratio of benzyne.

We have described here the first examples of photo-initiated cycloisomerizations of multi-yne substrates to form benzyne—the photochemical-HDDA (h ν -HDDA) reaction. This class of reaction was shown to be effective for a number of different tetrayne substrates that vary both in the nature of the aryl substituents on the terminus of each conjugated butadiyne subunit as well as in the type of atoms that compose the linkage between the two diynes. Each of the h ν -HDDA reactions described here was also performed thermally; in most cases, very little variation in isolated yields was observed (see Supporting Information for details). The behavior of the benzyne intermediates generated either photochemically or thermally was shown to give indistinguishable outcomes by several additional criteria, suggesting that the benzyne from each mode of activation was in identical rather than different electronic states. We speculate that this h ν -HDDA reaction could prove advantageous in activating benzyne chemistry in, for example, light-addressable settings or biological media.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1.

(a) The generic HDDA cascade. (b) Dihydrogen transfer—an example of a new class of trapping reaction.⁴ (c) The first hv-HDDA reaction vis-à-vis its thermal variant.

FIGURE 2.

(a) Structures of tetraynes **7b-i** that were studied (in addition to **7a**). (b) UV absorption spectra of several tetraynes (10^{-5} M in CHCl₃), showing effects of the remote substituent.

FIGURE 3.

(a) The generic *hν*-HDDA reaction of the bis-*p*-methoxycarbonylphenyl tetrayne **7b**. (b) Adducts from trapping benzyne **12** through cycloaddition reactions. (c) Adducts from trapping with heteroatomic agents.

FIGURE 4.

[‡] (a) Products arising from the $h\nu$ -HDDA reaction of the bis-arylated tetraynes **7d-7h**; each substrate has a malonate-derived linker unit (**M**). (b) Products demonstrating that tetraynes **7j-7l** (Fig. 2a), each with a linker unit other than the buttressed malonate, are competent substrates for the $h\nu$ -HDDA reaction. [‡]Experiments conducted in chloroform at ambient temperature; see SI for the wavelength of the light source used.

FIGURE 5.

Competitive formation of the two isomeric benzyne **35** and **35'** as revealed by the ratio of products **36:36'**. They are produced in the same ratio under both thermal and photochemical initiation.