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Cyclohexeno[3,4]cyclodec-1,5-diyne-3-ene: A Convenient Enediyne

Annadka Shrinidhi and Charles L. Perrin*

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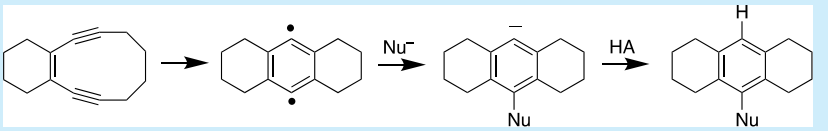
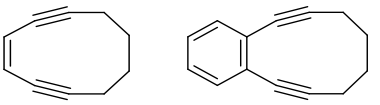


ABSTRACT: Enediynes are widely studied to understand their cycloaromatization and the trapping of the resulting *p*-dehydrobenzene diradical. However, few model substrates are known, and they are hard to synthesize and difficult to handle. Herein we report cyclohexeno[3,4]cyclodec-1,5-diyne-3-ene as a convenient model for studying the reactivity of enediynes. It can be easily synthesized from 1,2-diethynylcyclohexene and 1,4-diiodobutane. It is a solid that is stable at room temperature. In solution the *p*-dehydrobenzene diradical derived from its cycloaromatization can be trapped by nucleophiles. The rate-limiting step is the cyclization, which is slightly slower than that of the parent cyclodec-1,5-diyne-3-ene but faster than that of its benzo analogue, consistent with the distances between the reacting carbon atoms.

Enediynes are common scaffolds in medicinally important organic compounds.[1] However, the lability of their enediyne core limits their medicinal use because of cytotoxicity and nonspecificity, especially as anticancer antibiotics.[2] This behavior triggered studies toward understanding the reactivity of enediynes, particularly their cycloaromatization to form a *p*-dehydrobenzene ("*p*-benzyne", a term discouraged by IUPAC) diradical, a reaction known as the Bergman cyclization.[3] Many researchers have explored how the cyclization is affected by ring strain,[4] conformational and electronic effects,[5] and metal-ion coordination[6] in order to design enediynes for medicinal purposes.[1f,7] Most of those studies used model enediynes, either cyclodec-1,5-diyne-3-ene (**1**), its homologues, or its derivatives, such as 3,4-benzocyclodec-3-ene-1,5-diyne (**2**).[4a,8]



1 **2**

Some earlier studies explored the reaction of enediyne **1** with nucleophiles. The reaction of **1** with halides is first-order in enediyne and zeroth-order in both halide and carboxylic acid.[8b] Therefore, the rate-limiting step is the cycloaromatization, and the nucleophilic addition to the *p*-dehydrobenzene diradical is fast,[8c] as is protonation of the resulting "naked" aryl anion by water, carboxylic acid, or deuterated solvent.[8c] This mechanism is shown in Scheme 1 for a more general series of enediynes. The novel feature is the nucleophilic trapping of the diradical, in contrast to its expected reaction by radical pathways.

However, detailed studies of enediyne cycloaromatization, trapping of the resulting *p*-dehydrobenzene diradical, and the reactivity and selectivity of the aryl anion are challenging. One of the obstacles to thorough studies of enediyne **1** has been its low yield in synthesis. Jones et al. reported an isolated yield of 95% using an exceptional HMPA analogue "TEP" as an additive whose identity was never revealed.[9] In contrast, the synthesis of **1** using the more usual HMPA as the additive consistently produced a yield of only 5−10%.[10] An alternative but more circuitous procedure produced an overall yield of 12%.[4b] Furthermore, handling of **1** is challenging. It is a volatile and irritating liquid that is difficult to isolate. Because it decomposes within a day at room temperature, it must be stored in solution at −35 °C or below.

Therefore, alternative enediynes continue to be developed. Basak et al. studied the regioselectivity of nucleophilic addition to unsymmetrical diradicals derived from azaenediynes.[11] Many researchers studied enediyne **2**, for which a simple synthesis provides a 48% yield.[12] However, its disappearance does not follow simple first-order kinetics because it was observed that the efficiency of trapping of its *p*-dehydrobenzene diradical depends on the concentration of 1,4-cyclohexadiene.[12] Moreover, the kinetics are not zeroth-order in nucleophile.[10] Therefore, it can be concluded that the initial cycloaromatization must be reversible.

Another enediyne is desirable. An ideal candidate is cyclohexeno[3,4]cyclodec-1,5-diyne-3-ene (**3**, IUPAC name bicyclo[8.4.0]tetradeca-1,7-diyne-13-ene), a cyclohexene-fused cyclodec-1,5-diyne-3-ene. The additional alkylation increases

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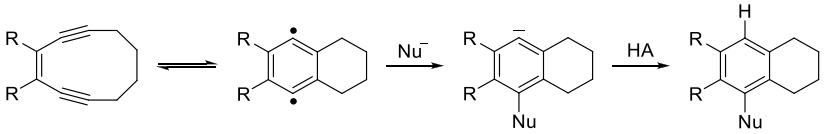
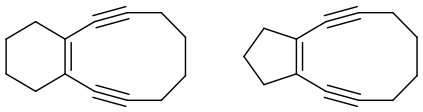
Scheme 1. Reactions of Enediynes 1 (R = H), 2 (RR = $(CH)_4$), and 3 (RR = $(CH_2)_4$)



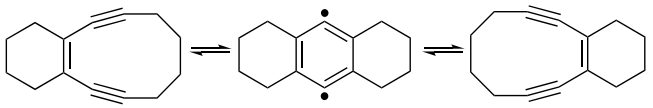
the stabilities of both the enediyne and its cycloaromatization product. Herein we report the robust synthesis of **3**, explore its cycloaromatization, study the reaction of nucleophiles with diradicals formed from **3**, and determine the kinetics of disappearance of **3**. We also report that cyclopentenoenediyne **4** has been too elusive.



3 **4**

Enediyne **3** has the further feature that reversal of the initial cycloaromatization can produce not only the original enediyne but also an identical isomer ("automer"), as shown in Scheme 2. In contrast, reversal of the cycloaromatization of enediyne **2**

Scheme 2. Degenerate Rearrangement of Enediyne 3



would produce a dienediyne, although no evidence was found for that complication.[12] Even if this rearrangement occurs for **3**, it cannot complicate the kinetics.

Synthesis

Enediyne **1** was prepared by cyclization of 1,10-dibromo-2,8-octadiyne via carbenoid coupling−elimination according to a modified procedure[10] derived from the reported literature.[9] Enediyne **2** was prepared by cyclization of 1,2-diethynylbenzene with 1,4-diiodobutane according to the literature procedure.[12] Enediyne **3** was prepared by cyclization of 1,2-diethynylcyclohexene with 1,4-diiodobutane. Details are provided in the Supporting Information. It was found to be an off-white solid with a melting point of 105−106 °C. It is stable under ambient conditions for more than a month and can be stored in powder form at −10 °C for more than a year with no apparent decomposition.

Kinetics

Enediyne was added to a solution of nucleophile X^- and pivalic acid (with added 1,4-cyclohexadiene for enediyne **2**) in DMSO-d_6 containing 1,3,5-trichlorobenzene as an internal standard. The sample was heated in an oil bath. Disappearance of the starting material was monitored every 1.0 h by removing the sample and analyzing it by ^{1}H NMR spectroscopy. The first-order rate constant k was obtained by least-squares analysis of a logarithmic plot of [enediyne] versus time (eq 1):

$$\ln([\mathbf{1}\text{–}\mathbf{3}]_t) = -kt + \ln([\mathbf{1}\text{–}\mathbf{3}]_0) \quad (1)$$

Rate constants k and free energies of activation ($\Delta G^{\ddagger}$) for the disappearance of enediynes **1**−**3** in the presence of LiX and pivalic acid in DMSO-d_6 are given in Table S1. Details are provided in the Supporting Information.

Results

In order to assign the rate-limiting step for the transformation of enediyne **3** plus nucleophile X^- to 9-X-1,2,3,4,5,6,7,8-octahydroanthracene (**5X**), we measured the kinetics of these reactions. The initial concentration of **3** was kept low while the concentration of nucleophile or acid was varied. Table 1 lists

Table 1. Rate Constants and Yields of 5X for Reactions of Enediyne 3 (5 mM) with MX and Pivalic Acid (HA) in DMSO-d_6 at 75°C

MX	$[X^-]_0$ (mM)	$[HA]_0$ (mM)	10^5k (s^{-1})	yield of **5X** (%)[a]
LiI	500	50	5.23	>99
LiI	250	25	5.21	>99
Bu_4NI	250	25	5.16	>99
LiBr	500	50	5.63	82
LiBr	250	25	5.60	83
Bu_4NBr	250	25	5.57	85
NaCN	500	50	5.78	78
NaCN	250	25	5.75	79
Bu_4NCN	250	25	5.70	81
KSCN	500	50	6.16	66
KSCN	250	25	6.12	68
Bu_4NSCN	250	25	6.03	69
none	0	50	8.43	43[b]

[a]Averages of ^{1}H NMR and GC-FID yields. [b]The product was **5H**.

the rate constants and yields of **5X** for reactions of enediyne **3** with MX in DMSO-d_6 containing pivalic acid. The first-order rate constants for these reactions at 75 °C lie between 5.1×10^{-5} and 6.2×10^{-5} s^{-1}.

The rate is independent of the concentrations of the nucleophile and acid but not entirely independent of the nucleophile. It is slightly lower than the rate of decomposition of enediyne **3** in the absence of nucleophiles. That is an indication that the variability is due to the incursion of polymerization, which occurs when the *p*-dehydrobenzene diradical reacts with the enediyne. Nucleophilic capture of the diradical prevents polymerization. According to computations,[8c] that capture is encounter-controlled, with no activation energy other than that required for desolvation of the nucleophile. Consequently, smaller ions, which are more strongly solvated, have a higher activation energy and are less effective in preventing polymerization. Therefore we conclude that the most reliable rate constant for cycloaromatization of **3** at 75 °C is $(5.20 \pm 0.025) \times 10^{-5}$ s^{-1}, as observed with I^- as the nucleophile, which most effectively intercepts the diradical before it can induce polymerization. Further studies with a mixture of competing nucleophiles will assess the role of solvation.

The data show that the observed rate constant for disappearance of enediyne **3** is independent of the concentration of the nucleophile. Therefore the reaction is simply first-order in [**3**] and zeroth-order in $[I^-]$. This is the same result as for **1**,[8c] for which it was concluded that the rate-limiting step is the initial cyclization to a *p*-dehydrobenzene

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Org. Lett. XXXX, XXX, XXX−XXX

diradical, which is attacked by nucleophile in a fast second step followed by rapid protonation of the "naked" aryl anion (Scheme 1).[8d]

The free energies of activation for the conversion of enediynes **1**−**3** to their diradicals were evaluated from the rate constants for enediyne decomposition in DMSO-d_6 in the presence of LiI and pivalic acid. The values are shown in Table 2.

Table 2. Free Energies of Activation for the Conversion of Enediynes 1−3 to the Corresponding *p*-Dehydrobenzene Diradicals

	1	2	3
$\Delta G^{\ddagger}$ (kcal mol^{-1})	25.3 ± 0.0	28.6 ± 0.1	27.2 ± 0.1
lit.	24.8,[4b] 27.4[13]	29.5[12]	–

For comparison with activation energies, calculated 1,6 distances between the two carbon atoms that form the new C−C bond during *p*-dehydrobenzene formation are given in Table 3.

Table 3. C1−C6 Distances (d) in Enediynes 1−3

	1	2	3
d (Å)	3.26	3.46	3.32
lit.	3.25[4b]	–	–

Discussion

By the use of Semmelhack's protocol,[12] macrocyclization of 1,2-diethynylcyclohexene with 1,4-diiodobutane produces enediyne **3** as a major product (45%). The fact that enediyne **3** is solid and stable under ambient conditions allows easy handling and accurate measurement of reactivity and kinetics.

Upon heating, the *p*-dehydrobenzene diradical generated from enediyne **1** reacts with nucleophiles such as I^-, SCN^-, Br^-, NC^-, and N_3^-.[8c] Similarly, the *p*-dehydrobenzene diradical generated from enediyne **2** reacts with I^-, SCN^-, and Br^-.[10] In order to study cycloaromatization and nucleophilic addition to the resulting *p*-dehydrobenzene diradical, enediyne **3** was heated with nucleophiles. With iodide, **3** reacts to form 9-iodo-1,2,3,4,5,6,7,8-octahydroanthracene **5I** in >99% isolated yield. It was found to be necessary to use a dilute solution of enediyne to reduce polymerization, and 5 mM was found to be optimal. Heating enediyne **3** without any nucleophile produced 1,2,3,4,5,6,7,8-octahydroanthracene (**5H**) in 40% yield, whereas no **5H** was formed in the presence of I^-. Consequently an excess of nucleophile was used during the reaction to promote the capture of the diradical. The reactions of **3** with SCN^-, Br^-, NC^-, and NO_2^- produced moderate to good yields of **5X** (Table 1). The lower yields of **5X** compared with **5I** are due to the lower nucleophilicity of X^-, leading to increased conversion to **5H** and other unidentified compounds (Figure S8).

The significant result in Figures S10 and S11 is that the rate of disappearance of enediyne **3** is effectively independent of the concentration of nucleophile or acid and regardless of which nucleophile is present. Thus, the rate law can be written simply as a first-order equation, $-d[\mathbf{3}]/dt = k[\mathbf{3}]$. It follows that the rate-limiting step is the cycloaromatization of **3** to form the *p*-dehydrobenzene diradical, which then reacts rapidly with the nucleophile to form product **5X**.

According to Table S1, the rates of disappearance of enediynes **1**, **2**, and **3** in the presence of LiI and pivalic acid decrease in the order **1** > **3** > **2**, and this trend remains the same even with varying $[I^-]$ or temperature. Figure 1 shows a

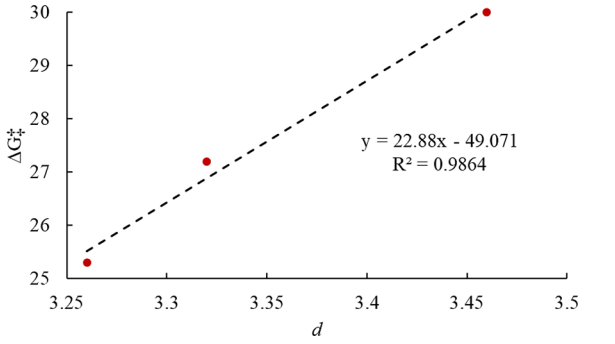

Figure 1. Free energy of activation (in kcal mol^{-1}) for conversion of enediynes **1**−**3** to the corresponding *p*-dehydrobenzene diradicals vs C1−C6 distance (in Å).

plot of the free energy of activation for cyclization of enediynes **1**, **2**, and **3** versus the calculated distance between carbon atoms C1 and C6, between which the new bond is formed (Tables 2 and 3). For enediyne **2**, $\Delta G^{\ddagger}$ was taken as 30 kcal mol^{-1} from data (Table S1) in the presence of Cl^-, which is least likely to add directly to **2**. The least-squares slope is 23 kcal mol^{-1} Å^{-1}, and the correlation coefficient R^2 is 0.99. Therefore, an 0.1 Å reduction in the distance between C1 and C6 is associated with a 2.3 kcal mol^{-1} reduction in activation energy.

The behavior of enediyne **2** is more complicated. According to the data in Table S1, the rate of disappearance of **2** increases upon doubling of the concentration of LiX, but by less than twofold. More significantly, the rate of disappearance of enediyne **2** is lower with the less nucleophilic LiBr and even lower with LiCl. No such variations are seen with **1** or **3**. We attribute these deviations from zero- or first-order dependence on halide to direct nucleophilic addition of halide to the C≡C bond of **2** as well as to its *p*-dehydrobenzene diradical. Moreover, **2** is slower to cyclize because cyclization produces a dehydronaphthalene diradical, which gains less aromatic stabilization than for **1** and **3**, which produce a dehydrobenzene from a nonaromatic precursor. Therefore, the plot in Figure 1 is not necessarily linear because the aromatic stabilization is not constant, and the point for **2** may be higher if **2** reacts directly with Cl^- or if capture of dehydronaphthalene diradical by I^- is competitive with its recyclization. Nevertheless, the plot is treated as linear for simplicity.

It is not surprising that the rate of cyclization correlates with the C1−C6 distance. Nicolaou et al. reported that saturation of the double bond following intramolecular thiol addition to the α,β-unsaturated ketone in calicheamicin-γ_1 shortens the calculated distance between the alkyne carbons. Specifically, they reported that the shorter C1−C6 distance between alkyne carbons in the cyclic aglycone (3.16 Å) increases the chance of spontaneous cyclization relative to the acyclic aglycone (3.35 Å).[4a] They also performed calculations on several other cyclic enediynes and proposed that the critical C1−C6 distance (d_c) for room-temperature cyclization is 3.20−3.31 Å.[4b] Later work suggested that this range may be extended to 2.9−3.4 Å.[14] Furthermore, the synthesis of model cyclic enediynes with

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varying tendencies toward cycloaromatization due to varying C1−C6 distances provided evidence for this trend. Indeed, enediyne **3**, with d_c = 3.32 Å, is stable at room temperature. It was further demonstrated that the critical factor for ease of cyclization is more accurately described as the difference between the strain energies of ground and transition states, in part because there is a repulsive contribution from the in-plane π orbitals.[15]

In summary, enediyne **3** undergoes cycloaromatization at a convenient 65−75 °C, slightly higher than the 45−55 °C for **1** but lower than the 85−95 °C for **2**, and these differences can be understood in terms of the structures of those enediynes.

Conclusions

We have demonstrated that cyclohexeno[3,4]cyclodec-1,5-diyne-3-ene (**3**) is a convenient model for the study of the reactivity of enediynes. It was synthesized in a relatively good yield and is stable for more than a month at room temperature. The first-order rate constant for its disappearance at 75 °C is $(5.4 \pm 0.1) \times 10^{-5}$ s^{-1} independent of the nucleophile concentration. Therefore, as with cyclodec-1,5-diyne-3-ene (**1**), the *p*-dehydrobenzene diradical derived from **3** reacts rapidly with nucleophiles. Comparison of the activation energies for cyclization of enediynes **1**, **2**, and **3** shows that they parallel the critical C1−C6 distance across which the bond forms.

Enediyne **3** is a valuable addition to the suite of enediynes that probe not only their cycloaromatization but also the unusual nonradical reaction between nucleophiles and the *p*-dehydrobenzene diradical, as well as the reactivity and selectivity of the resulting aryl anion. These are reactions that can now be more easily probed with this more readily available enediyne.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02459.

Details on materials and instrumentation; synthetic procedures and characterization; procedures for kinetics, free energy of activation, molecular mechanics, ^{1}H NMR analysis, and GC−MS analysis; spectra; plots of $[\mathbf{3}]_t/[\mathbf{3}]_0$ and ln $[\mathbf{3}]_t/[\mathbf{3}]_0$; first-order rate constants and free energies of activation for the disappearance of enediynes **1**−**3**; and calculated distances, bond angles, and strain energies in their MM2 energy-minimized structures (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Charles L. Perrin − *Department of Chemistry, University of California—San Diego, La Jolla, California 92093-0358, United States;* orcid.org/0000-0001-5732-5330; Email: cperrin@ucsd.edu

Author

Annadka Shrinidhi − *Department of Chemistry, University of California—San Diego, La Jolla, California 92093-0358, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c02459

Author Contributions

A.S. designed and performed all of the experiments. A.S. and C.L.P. wrote the manuscript. C.L.P. supervised the work.

Notes

The authors declare no competing financial interest.

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Org. Lett. XXXX, XXX, XXX−XXX