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Syntheses, structure, and reactivity of acyclic enetriyne and enetetrayne derivatives

John D. Spence [a,*], Miranda L. Lackie [a], Nicola A. Clayton [a], Sergio A. Toscano [a], Michelle A. Farmer [a], Esfir Popova [a], Marilyn M. Olmstead [b]

[a] Department of Chemistry, California State University, Sacramento, 6000 J Street, Sacramento, CA 95819, United States
[b] Department of Chemistry, University of California, Davis, One Shields Avenue, Davis, CA 95616, United States

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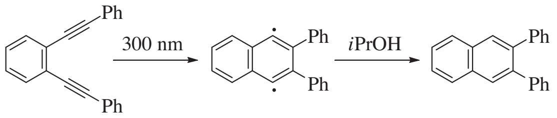
ABSTRACT

Sonogashira coupling of buta-1,3-diynylbenzene with ((2-iodophenyl)ethynyl)trimethylsilane and 1,2-diiodobenzene led to the novel enetriyne, 1-ethynyl-2-(phenylbuta-1,3-diynyl)benzene, and enetetrayne, 1,2-bis(phenylbuta-1,3-diynyl)benzene, respectively. Solid state structural and thermal analyses are also described. In solution, 1-ethynyl-2-(phenylbuta-1,3-diynyl)benzene was found to undergo thermal Bergman cyclization to afford 2-(phenylethynyl)naphthalene.

Highly conjugated carbon rich compounds derived from (*E*)-, (*Z*)-, and *gem*-diethynylethenes and tetraethynylethene have found widespread interest for applications in molecular electronics, nonlinear optics, and light-emitting diodes in addition to their use in the preparation of larger macrocycles and cages through organometallic coupling reactions.[1] Cyclization pathways are also available to the diethynylethene unit, most notably Bergman[2] and related cycloaromatizations[3] of (*Z*)-hex-3-ene-1,5-diyne units to the corresponding 1,4-didehydrobenzene diradical, providing additional applications in synthetic and medicinal chemistry as DNA cleaving agents. It is widely recognized that the naturally occurring enediyne antitumor agents employ strain control to modulate the reactivity of a cyclic enediyne unit leading to their cytotoxic properties.[4] In addition to being promoted thermally, photochemical activation of cyclic[5] as well as acyclic enediynes derived from 1,2-bis(phenylethynyl)benzene[6] can be accomplished upon irradiation at 300 nm to control the timing of resultant Bergman cyclization (Scheme 1).[7] (*E*)-Hex-3-ene-1,5-diyne lacks this reactivity while, with appropriate aryl substituents, cross-conjugated geminal diethynylethene units can undergo a Hopf-type cyclization[8] under thermal conditions,[9] radical anionic Bergman-like cyclization under reductive conditions,[10] or photochemical electrocyclic ring closure.[11] Tetraethynylethene, despite possessing a bis(enediyne) motif, has not been reported to undergo cyclization reactions.



Scheme 1. Bergman cycloaromatization of 1,2-bis(phenylethynyl)benzene.

Recently, we have been interested in highly conjugated enediynes to examine how extended conjugation affects chemical and physical properties of the enediyne unit.[12] One method to extend conjugation to the enediyne core is to incorporate additional alkyne units through the enediyne alkyne, generating buta-1,3-diynyl derivatives. Such butadiynyl enediyne derivatives have been previously explored in the literature (Fig. 1), but none have led to isolation of the corresponding Bergman cyclization product. Systems studied include the bis(enediyne) **1**[13] with a central butadiyne linkage and related cyclic derivatives,[14] cyclodec-5-en-1,3,7,9-tetrayne analogs such as **2**,[13] dehydrobenzoannulenes[15] including **3**[16] and **4**,[17] bis(buta-1,3-diynyl)pyridines **5**,[18] and the related non-conjugated enetetrayne **6**.[19] Of these systems, only acyclic **1** was observed to give a Bergman cycloaromatization product based on mass spectroscopy data. Skipped enetetrayne **6** was found to undergo a complex tandem radical cyclization initiated by formation of a non-benzenoid five-membered ring diradical. For the cyclic derivatives, calculations suggest strain build up in the transition state prevents cycloaromatization of the enediyne.[13] The thermal reactivity of 2,3-bis(buta-1,3-diynyl)pyridines was

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* Corresponding author. Tel.: +1 (916) 278 4477; fax: +1 (916) 278 4986.
E-mail address: jspence@csus.edu (J.D. Spence).

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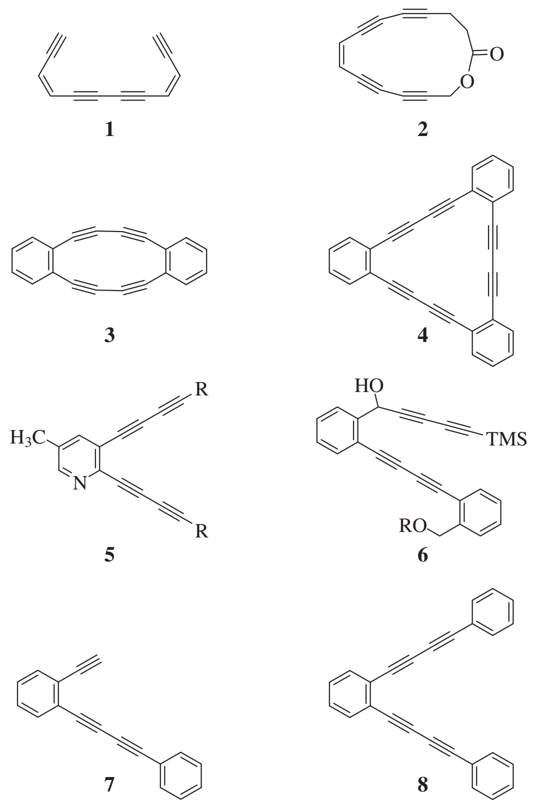


Figure 1. Examples of buta-1,3-diynyl enediyne derivatives.

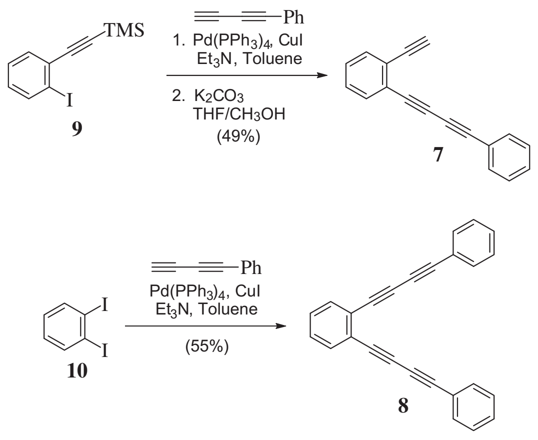
not reported. Furthermore, no photochemical studies have been reported for enetetrayne models. In this paper, we describe the synthesis of an acyclic enetriyne **7** and enetetrayne **8** containing phenylbuta-1,3-diynyl units to examine structure and reactivity of the extended enediyne unit.

The synthetic route toward acyclic enetriyne and enetetrayne derivatives presented herein employed straightforward Sonogashira cross-coupling[20] reactions of buta-1,3-diynylbenzene outlined in Scheme 2. Due to the relative instability of the terminal buta-1,3-diynylbenzene, however, a solution of this key intermediate in toluene was freshly prepared from 2-methyl-6-phenylhexa-3,5-diyn-2-ol as previously described,[21] and immediately used in subsequent Sonogashira coupling. Pd/Cu-catalyzed coupling employing a two-fold excess of buta-1,3-diynylbenzene with ((2-iodophenyl)ethynyl)trimethylsilane **9**[22] followed by desilylation with K_2CO_3 in THF/MeOH readily afforded enetriyne **7** in a two-step 49% yield. In a similar fashion, Sonogashira coupling employing a four-fold excess of buta-1,3-diynylbenzene with 1,2-diiodobenzene **10** afforded enetetrayne **8** in 55% yield. Enetriyne **7** and enetetrayne **8**, isolated as stable solids, were purified by column chromatography and recrystallized prior to examining thermal and photochemical properties.

The electronic absorbance spectra of enetriyne **7** and enetetrayne **8** in $CHCl_3$ each gave three prominent absorption bands above 300 nm, with the longest wavelength absorbance red-shifted compared to their respective enediyne counterparts. For enetriyne **7**, the longest wavelength absorbance was observed at 340 nm (ε = 22,400), while the most intense absorption was observed at 243 nm (ε = 37,400). Similarly, the longest wavelength absorbance for enetetrayne **8** was observed at 352 nm (ε = 19,400), with a weak shoulder to the red, and the wavelength of maximum intensity at 251 nm (ε = 41,400). The analogous enediyne, 1,2-bis(phenylethynyl)benzene, gave one prominent peak above 300 nm observed at 310 nm with a weak shoulder to the red, and most intense absorption at 273 nm. Stronger absorbance to higher excited states, as observed for enetriyne **7** and enetetrayne **8**, is a common feature for enediyne chromophores.[23] The emission spectra of enetetrayne **8**, however, were extremely weak compared to the parent enediyne 1,2-bis(phenylethynyl)benzene. Upon excitation at 313 nm, enetetrayne **8** gave a relative fluorescence quantum yield of only 0.02 compared to 0.57 for 1,2-bis(phenylethynyl)benzene using perylene ($\Phi_{\rm fl}$ = 0.94) as a reference. Enetriyne **7** shows no measurable fluorescence.

To gain further insight into the structure of the butadiynyl derivatives we obtained the X-ray crystal structures of enetriyne **7** and enetetrayne **8** illustrated in Figure 2. Selected bond lengths and angles are provided in Table 1. As illustrated in Figure 2, the phenylbutadiynyl units of enetetrayne **8** are more widely splayed than the corresponding alkynyl units of enetriyne **7**, leading to a larger observed c··d distance for **8** (4.297 Å) compared to **7** (4.039 Å). Additionally, the entire molecule of enetriyne **7** is essentially planar with a 6.4° angle between phenyl rings, whereas in enetetrayne **8** the distal phenyl substituents are twisted by 74.3° and by 71.6° with respect to the central phenyl ring.

Thermal reactivity of enetriyne **7** and enetetrayne **8** in the solid state has been investigated by differential scanning calorimetry (DSC). Although DSC has been shown to be a very crude measure of relative reactivities for enediynes,[24] and gives no information regarding cyclization pathway, it provides insight into thermal stability and potential for cyclization in solution. **7** and **8** each displayed melting endotherms followed by broad exotherms indicative of radical cyclization and subsequent polymerization. For



Scheme 2. Synthesis of enetriyne **7** and enetetrayne **8**.

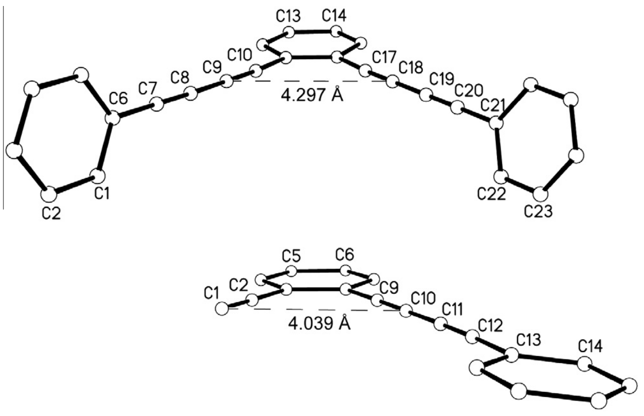
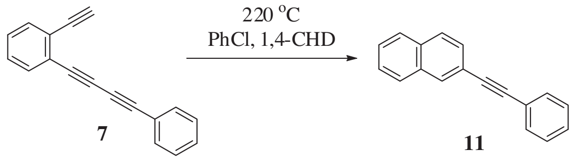


Figure 2. X-ray crystal structures of enetriyne **7** and enetetrayne **8**.

Table 1
Selected bond lengths (Å) and bond angles (°) for enetriyne **7** and enetetrayne **8**

*Enetriyne **7***			
C1–C2	1.1859(18)	C1–C2–C3	178.86(12)
C2–C3	1.4385(16)	C2–C3–C8	120.23(19)
C3–C8	1.4145(15)	C3–C8–C9	119.71(10)
C8–C9	1.4318(15)	C8–C9–C10	179.36(12)
C9–C10	1.2072(15)	C9–C10–C11	179.23(12)
C10–C11	1.3707(15)	C10–C11–C12	178.54(12)
C11–C12	1.2059(15)	C11–C12–C13	177.74(11)
C12–C13	1.4309(15)		
C1–C10 (c··d)	4.039(2)		
*Enetetrayne **8***			
C7–C8	1.209(2)	C6–C7–C8	179.46(17)
C8–C9	1.380(2)	C7–C8–C9	178.84(18)
C9–C10	1.201(2)	C8–C9–C10	179.28(17)
C10–C11	1.438(2)	C9–C10–C11	176.11(17)
C11–C16	1.413(2)	C10–C11–C16	121.36(14)
C16–C17	1.442(2)	C11–C16–C17	121.43(14)
C17–C18	1.198(2)		
C18–C19	1.378(2)		
C19–C20	1.205(2)		
C20–C21	1.438(2)		
C9–C18 (c··d)	4.297(3)		



entry[a]	[CHD] (M)	time (h)	conversion (%)[b,c]	yield (%)[c]
1	0.047	4	13	-
2	0.47	4	19	5 (24)[d]
3	2.35	4	30	12 (40)[d]
4	0.047	12	34	-
5	0.47	12	52	12 (24)[d]
6	2.35	12	82	35 (43)[d]

[a] Initial [**7**] = 4.7 × 10^{-3} M. [b] Based on recovered starting material.
[c] Measured by GC with internal standard. [d] Based on recovered **7**.

Scheme 3. Thermal Bergman cycloaromatization of enetriyne **7**.

enetriyne **7**, a melting endotherm was observed at 64 °C followed by a strong exotherm with a peak maximum at 174 °C. The exotherm temperature maximum for **7** is nearly 20 °C lower than that observed for 1-ethynyl-2-phenylethynylbenzene (193 °C), and is slightly higher than that observed for 1,2-diethynylbenzene (166 °C). Enetetrayne **8** displays a much higher melting endotherm at 139 °C, followed immediately by a broad exotherm at 190 °C. In comparison, 1,2-bis(phenylethynyl)benzene displays a much higher exotherm peak temperature at 323 °C. The DSC data suggests sterics and strain build-up in transition state is not an issue for thermal Bergman cyclization of acyclic enetriyne **7** and enetetrayne **8** as observed cyclization temperatures are comparable to 1,2-diethynylbenzene which readily undergoes solution cyclization to afford naphthalene.[24]

To determine if enetriyne **7** and enetetrayne **8** are capable of undergoing Bergman cyclization their solution reactivity was examined in the presence of a hydrogen atom donor. Heating a solution of enetriyne **7** in chlorobenzene containing 10–500 fold excess of 1,4-cyclohexadiene (CHD) at 180 °C for 24 h led primarily to recovery of unreacted starting material with trace amounts of cyclized product observed by GCMS and ^{1}H NMR spectroscopy. Upon increasing the reaction temperature to 220 °C, however, enetriyne **7** was found to undergo Bergman cyclization to produce naphthalene derivative **11** as a function of 1,4-cyclohexadiene concentration (Scheme 3). While traces of **11** were observed with 10 equiv of 1,4-cyclohexadiene, increased yields were observed with 100 and 500 equiv of hydrogen atom donor indicative of a highly endothermic and reversible Bergman cyclization as previously observed for benzannelated enediynes.[24,25] On a preparative scale, the cyclization of **7** in the presence of 500 molar equivalents of 1,4-cyclohexadiene led to the isolation of pure **11** in 11% yield upon heating for 18 h at 220 °C. Further increase of reaction temperature and amount of hydrogen atom donor, including conducting the reaction in neat 1,4-CHD, did not lead to any improvement in the isolated yield of **11**. The cyclization of **7** and isolation of **11** is an improvement compared to the cyclization of compound **1** in which the product, biphenyl, was only observed by GCMS data with no isolated yield reported.[13] The isolated yield of **11**, however, is lower than the 35% isolated yield of naphthalene from the thermal Bergman cyclization of 1,2-diethynylbenzene.[24] Under similar conditions (100–500 fold excess 1,4-CHD, chlorobenzene, 220 °C), enetetrayne **8** showed degradation of starting material, however, no evidence of products derived from single or double Bergman cyclization were observed. In addition, products derived from rearrangement of the initial 1,4-diradical and C1–C5 derived cyclization products, observed in the thermal cyclization of 1,2-bis(phenylethynyl)benzene,[26] were not observed in the thermal cyclization of **7** or **8**.

Irradiation of **7** and **8** in isopropanol at 300 and 350 nm[27] led to rapid conversion of starting material, however, no isolable products were observed for either enetriyne **7** or enetetrayne **8**. Trace amounts of volatile products resulting from addition of a molecule of solvent were observed by GCMS; however, it is unclear if these are a result of Bergman cyclization or photoreduction of one of the alkynyl units followed by solvent addition. Similar results were obtained in alternative solvents commonly employed in photo-Bergman cyclizations including acetonitrile, benzene, and tetrahydrofuran in the presence or absence of 1,4-CHD as hydrogen atom donor. As photo-Bergman cyclization is favored through the excited singlet state,[6] the weaker fluorescence of **7** and **8** compared to 1,2-bis(phenylethynyl)benzene indicates alternative reaction pathways for **7** and **8** through the triplet excited state.

In effort to promote photo-Bergman cyclization at 350 nm, we prepared acyclic enetriyne **7** and enetetrayne **8** containing phenylbutadiynyl units. With extended conjugation, each derivative shows absorption bands out to 340–350 nm, though extremely weak to no fluorescence was observed. The presence of additional alkyne units reduces the ability of the core enediyne to undergo Bergman cyclization and favors alternative polymerization or degradation pathways. Enetriyne **7** is the first reported example of an extended enediyne containing a butadiynyl unit to afford the isolated thermal Bergman cyclization product, however, no photo-Bergman cyclization products were observed for **7** or **8**.

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Supplementary data

Experimental conditions and spectral data for compounds **7**, **8**, and **11**. Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 964855 for **7** and CCDC 964854 for **8**. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.Uk).

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.01.076.

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27. Photolysis experiments were conducted in a Rayonet photochemical reactor equipped with 16 3000 Å or 3500 Å lamps. A quartz vessel containing a degassed solution of 7 or 8 (20 mg sample in 100 mL solvent) was irradiated for 3–12 h.