Photochemical Rearrangement of Enediynes: Is a "Photo-Bergman" Cyclization a Possibility?

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Abstract: The enediynes **1** and **2** were photolyzed in 2-propanol to yield products akin to those analogous to a thermal Bergman cyclization mechanism. In addition, products resulting from photoreduction of one of the triple bonds of the enediyne functionality are also formed. The product distributions and yields were found to be dependent on the substituents on the triple bonds and on the nature of the double bond; in particular, phenyl substituents on the triple bonds eliminated the photoreduction products, and overall yields were higher when the double bond of the enediyne was of aromatic character. Triplet sensitization studies and laser flash photolysis experiments point toward radical mechanisms taking place during formation of both classes of products, with the photoreduction products forming from the excited triplet state and the cyclized naphthyl products forming from either the singlet or the triplet states. For the cyclization reaction, a substituted 1,4-dehydronaphthalene biradical species, structurally identical to a hypothetical Bergman biradical, is suggested to be the most likely intermediate.

Introduction

The chemistry of enediynes has been an area of avid scientific interest during the past two decades, as a result of its application in the design of a class of potent antitumor antibiotics.[1−8] For example, the drugs calicheamicin, dynemicin, and esperamicin, each of which possesses an enediyne unit, have been extensively studied, and have been shown to produce a highly reactive aromatic 1,4-biradical intermediate, which is responsible for the biological activity. Such intermediates were first characterized by Bergman,[9] who trapped the resulting *p*-benzyne biradical upon thermolysis of an acyclic enediyne. Since then the thermal rearrangement, commonly referred to as the Bergman rearrangement, has been thoroughly explored both experimentally and theoretically,[10−17] and both the thermodynamic and kinetic properties of the thermal cyclization are becoming better understood. However, despite the fact that both double and triple bonds display rich photoreactivities, comparatively very few reports on the photochemistry of enediynes exist in the literature. The first related study was conducted in 1967,[18,19] whereupon diynes were shown to yield intermolecular adducts. The first intramolecular photochemical rearrangement of enediynes to yield a cyclized product was discovered by accident in 1968;[20] however, no further activity in this field took place until almost two decades later, when enediynes were shown during photosensitization to undergo cis,trans-isomerization around the double bond,[4] as well as to cleave DNA strands,[21,22,24] although the mechanism of neither process has been elucidated.

In 1994 we reported the photosensitized reaction of an aromatic enediyne to afford a cyclized naphthyl product, possibly via a 1,4-dehydronaphthalene intermediate akin to that expected from a thermal Bergman rearrangement [23] (Scheme 1). Following our report, in 1996 Funk and co-workers[24] reported the photochemistry of a series of aromatic enediyne molecules, which were found to yield a Bergman-type cyclized product in the presence of 1,4-cyclohexadiene as a hydrogen donor; moreover, water-soluble analogues of the enediynes studied were found to be effective in binding to DNA and in

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(1) Nicolaou, K. C.; Liu, A.; Zeng, Z.; McComb, S. *J. Am. Chem. Soc.* **1992**, *114*, 9279−9284.

(2) Nicolaou, K. C.; Dai, W.; Wendeborn, S. V.; Smith, A. L.; Tirisawa, Y.; Maligres, P.; Hwang, C. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1032−1036.

(3) Nicolaou, K. C.; Smith, A. L. *Acc. Chem. Res.* **1992**, *25*, 497−503.

(4) Kagan, J.; Wang, X.; Chen, X.; Lau, K. Y.; Batac, I. V.; Tuveson, R. W.; Hudson, J. B. *J. Photochem. Photobiol. B: Biol.* **1993**, *21*, 135−142.

(5) Nicolaou, K. C.; Ogawa, Y.; Zuccarello, G.; Kataoka, H. *J. Am. Chem. Soc.* **1988**, *110*, 7247−7248.

(6) Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1377−1500.

(7) Wender, P. A.; Zercher, C. K.; Beckham, S.; Haubold, E.-M. *J. Org. Chem.* **1993**, *58*, 5867−5869.

(8) Golik, J.; Clardy, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Okhuma, H.; Saitoh, K. *J. Am. Chem. Soc.* **1987**, *109*, 3461−3462.

(9) Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25−30.

(10) Yoshida, K.; Minami, Y.; Azuma, R.; Saeki, M.; Otani, T. *Tetrahedron Lett.* **1993**, *34*, 2637−2640.

(11) Kraka, E.; Cremer, D. *J. Am. Chem. Soc.* **1994**, *116*, 4929−4936.

(12) Lockhart, T. P.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4091−4096.

(13) Lott, W. B.; Evans, T. J.; Grissom, C. B. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2583−2586.

(14) Myers, A. G.; Dragovich, P. S.; Kuo, E. Y. *J. Am. Chem. Soc.* **1992**, *114*, 9369−9386.

(15) Gleiter, R.; Kratz, D. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 842−845.

(16) Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660−661.

(17) Lindh, R.; Perrson, B. J. *J. Am. Chem. Soc.* **1994**, *116*, 4963.

(18) Ipaktschi, J.; Staab, H. A. *Tetrahedron Lett.* **1967**, *45*, 4403−4408.

(19) Bossenbroek, B.; Shechter, H. *J. Am. Chem. Soc.* **1967**, *89*, 7111−7112.

(20) Campbell, I. D.; Ellington, G. *J. Chem. Soc. (C)* **1968**, *1968*, 2120−2121.

(21) Shiraki, T.; Sugiura, Y. *Biochemistry* **1990**, *29*, 9795−9798.

(22) Uesawa, Y.; Kuwahara, J.; Sugiura, Y. *Biochem. Biophys. Res. Commun.* **1989**, *164*, 903−911.

(23) Turro, N. J.; Evenzahav, A.; Nicolaou, K. C. *Tetrahedron Lett.* **1994**, *35*, 8089.

(24) Funk, R. L.; Young, E. R. R.; Williams, R. M.; Flanagan, M. F.; Cecil, T. L. *J. Am. Chem. Soc.* **1996**, *118*, 3291−3292.

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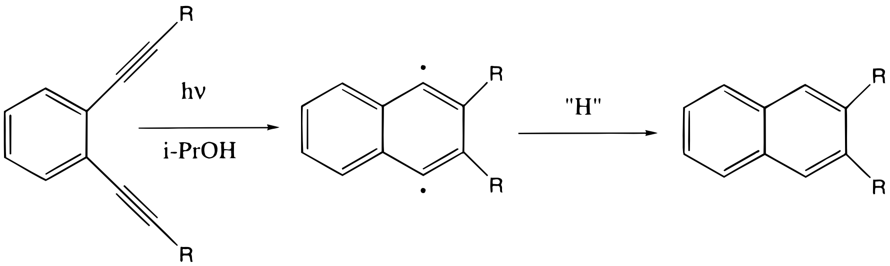
Scheme 1



cleaving single DNA strands upon irradiation. Suprisingly, no other example of a direct photochemical reaction of enediynes has been reported. The mechanistic study of photosensitized electron transfer rearrangements of an aromatic enediyne has also been recently reported,[25] but these reactions have been shown to yield different products than those expected from a hypothetical thermal case analogous to the Bergman rearrangement.

The induction of a Bergman cyclization of enediynes via a photochemical mechanism would be of great interest for a number of reasons. First, the observation of a photochemical reaction of enediynes to yield intermediates and products akin to those expected from a thermal Bergman rearrangement would provide yet another example of unsaturated organic molecules which undergo rearrangements via both thermal and photochemical mechanisms, such as the Diels−Alder reaction. Moreover, a photoinduced Bergman cyclization could have potential application in the design and activity of new enediyne-based antitumor drugs; whereas the current antibiotics are activated thermally at physiological temperature, a photolytic mechanism would allow a time-controlled activation of the drug by selective exposure to cell-permeable photons. With the rapid advances in the field of photodynamic therapy, such a possibility is becoming increasingly feasible and attractive. Furthermore, a photochemical enediyne cyclization could also exhibit potential in the design and preparation of new polymeric materials. Enediyne polymers have been shown to possess rather striking spectroscopic properties very different from those displayed by the monomers themselves.[15] Photosensitized cyclization of such polymer matrices can lead to the formation of new polymers containing a high degree of aromaticity and distinct properties without the need for high temperatures or strong reagents.

To examine whether a photoinduced reaction of enediynes is possible, and whether the reaction proceeds in a fashion comparable to the thermal case, the enediynes **1** and **2** were prepared and their photochemistry explored. The structures of these compounds possess the attractive features of (i) facile synthesis from readily available starting materials, (ii) elimination of cis,trans-isomerization of the double bond which is locked into a cis conformation by confinement in a ring, (iii) chromophores which would enhance light absorption and allow for "tracking" via spectroscopic methods, and (iv) thermal stability at slightly elevated temperatures which occur during irradiation with light. Furthermore, the variation of the nature of the double bond as well as the substituents on the triple bonds of the enediynes would elucidate the effect of the structure on the photochemical reactivity.

We report herein the successful photochemical induction of the reaction of enediynes **1** and **2**. In particular, we find that **2** yields the naphthyl derivative **2P**, expected from a hypothetical thermal Bergman cyclization, as the only product of photolysis, whereas **1** yields the Bergman-type product and additionally products arising from triple bond photoreductions. Furthermore, we find that not only the types of products but also the yields of cyclization are dependent on the structure of the parent compound. From the results of flash photolysis experiments, we rationalize the formation of the cyclized products as arising from a 1,4-aromatic biradical in analogy to a thermal mechanism.

Experimental Section

The enediynes **1** and **2** were synthesized via a copper coupling reaction of the appropriate dihaloalkene with an excess of 2 equiv of the alkyne;[1] in particular, these consisted of 1,2-diiodobenzene and 1-propyne for **1**, and 1,2-diiodobenzene and phenylacetylene for **2**. Both **1**[23] and **2**[25] have been previously prepared and characterized. All products were purified by flash column chromatography on silica gel with hexane as eluent; in some cases, multiple column purifications were run until over 99% purity by GC was achieved. **1**: ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ 1.05 (t, 6H); 1.5 (m, 4H), 2.42 (t, 4H), 7.18 (m, 2H), 7.35 (m, 2H); GCMS (70 eV EI, 1 peak) *m/z* 210; high-resolution MS (70 eV EI) *m/z* 210.1402 (estimated *m/z* 210.1409; error −3.3 ppm); UV/vis max (hexane) (M^{-1} cm^{-1}): $\epsilon_{292} \sim 480$, $\epsilon_{300} \sim 280$, $\epsilon_{308} \sim 80$, and $\epsilon_{313} \sim 30$. **2**: ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ 7.3 (m, 10H), 7.58 (m, 4H); GCMS (70 eV EI, 1 peak) *m/z* 278; high-resolution MS (70 eV EI) *m/z* 278.1103 (estimated *m/z* 278.1096; error +2.7 ppm); UV/vis max (hexane) (M^{-1} cm^{-1}): $\epsilon_{260} \sim 55500$, $\epsilon_{272} \sim 81500$, $\epsilon_{300} \sim 22800$, $\epsilon_{308} \sim 24700$, $\epsilon_{330} \sim 10700$.

Photolysis experiments were carried out with either a Rayonette Photochemical Reactor, equipped with eight 3000 Å lamps, or a medium-pressure Hanovia mercury lamp. In the latter case, a potassium chromate filter solution was employed to filter out wavelengths below 313 nm. Analytic irradiations were performed in test tubes and a "merry-go-round" apparatus was employed to ensure equal average light absorption by all samples. Irradiation runs contained pentadecane as an internal standard and were analyzed by gas chromatography on a Hewlett-Packard 5890 equipped with a SE-30 column and a flame ionization detector. For all irradiations, the solutions' optical density at the wavelength of irradiation was above 1. Samples were deoxygenated by purging with argon for 10−15 min. Preparative scale irradiations were performed for identification of the products. In this case, the products were separated by column chromatography and characterized by their mass and NMR spectra, and the GC retention times of the separated products were compared to those of the analytic runs. A Varian 200 MHz NMR spectrophotometer and a Hewlett-Packard 5890 GC Series II, equipped with a HP5972 mass spectral detector, were used.

UV/vis absorption spectra were recorded on a Hewlett-Packard 8452A diode array spectrophotometer. Fluorescence spectra were recorded on an LS-5 or an IAS Fluoromax-2 spectrophotometer. Quantum yields of fluorescence for **1** and **2** were determined by comparison to a solution of 9,10-diphenylanthracene by matching the optical densities at the excitation wavelength and comparison of the integrated area for the two spectra. In this manner, fluorescence quantum yields of approximately 0.04 and 0.4 were estimated for **1** and **2**, respectively. Phosphorescence spectra were measured on an LS-50 spectrophotometer. The energies of the excited singlet and triplet states of compounds **1** and **2** were determined from the (0,0) band of

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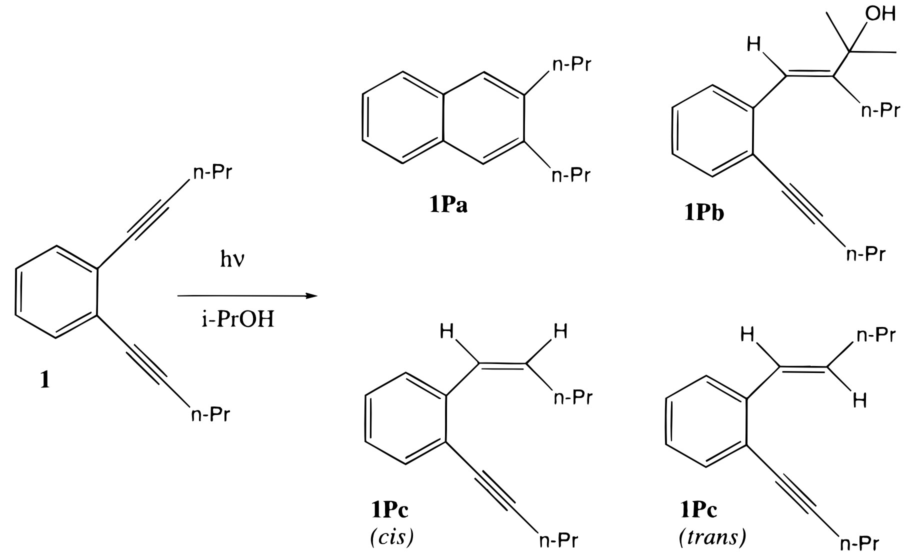
[25] Ramkumar, D.; Kalpana, M.; Varghese, B.; Sankararaman, S. *J. Org. Chem.* **1996**, *61*, 2247−2250.

Scheme 2



the low-temperature fluorescence and phosphorescence spectra, and were found to be 92 and 67 kcal/mol for **1** and 81 and 56 kcal/mol for **2**, respectively. For the low-temperature spectroscopies, the cell compartment of the instrument was fitted with a Dewar modified with a quartz cell bottom, to allow the incident light to pass through. The samples were contained in the Dewar filled with liquid nitrogen in quartz 5 mm NMR tubes. Background spectra of the Dewar setup lacking the sample were recorded during each experiment for reference.

Flash photolysis experiments were performed at room temperature by using the 308 nm output of a MPB Technologies AQX-150 XeCl excimer laser (ca. 2 mJ/pulse, 20 ns fwhm) for excitation of the enediynes, or the 355 nm output of a Continuum Surelite I Nd:YAG laser (ca. 8 mJ/pulse, 20 ns fwhm) for excitation of xanthone in the triplet sensitization studies. Samples were prepared with an optical density of 0.3 at the excitation wavelength, and were excited in 1 × 1 Suprasil quartz cells, after deoxygenating by purging with argon. Oxygen saturation of the solutions for quenching measurements was achieved by bubbling the solutions with oxygen. For the sensitization and quenching experiments, argon saturated static samples were employed, and a fresh solution was used for each quencher concentration. Typically 5−10 pulses were employed for each decay trace. Transient absorption spectra employed a flow system so as to ensure that a fresh volume of sample was irradiated with each pulse.

All solvents used were of spectroscopic grade, and the absence of absorbing species at the wavelength of irradiation was ensured by UV/vis spectroscopy.

Results

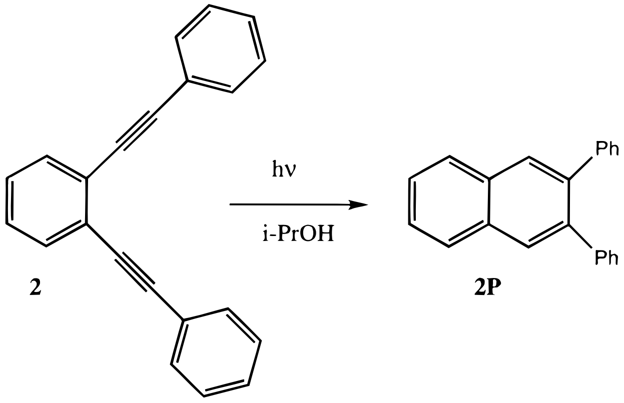
Steady-state photolysis of a 5 mM solution of **1** in 2-propanol affords the products **1Pa**, **1Pb**, and *cis*- and *trans*-**1Pc** in a ratio of approximately 2:4:2:1 (Scheme 2). When the reaction is carried out to 50% conversion of **1**, a yield of 25% for the cyclized **1Pa** and a mass balance of 80% are achieved; at higher conversions it is likely that intermolecular reactions yielding high molecular weight products not discernible by GC must be formed, as evidenced by a rapid decrease in the mass balance. In the presence of 1,4-cyclohexadiene, photolysis of **1** yields **1Pa** as well as a product whose mass spectrum is consistent with a reduction product containing an equivalent of the hydrogen donor. Moreover, although **1** photochemically converts in ethanol, *sec*-butanol, and *tert*-butanol, formation of **1Pa** and other products detectable by GC are only observed during photoreaction in the first alcohol. When the reaction of **1** is triplet sensitized by the irradiation of xanthone or acetophenone, both of whose triplet energies are higher than that of the enediyne, conversion is increased compared to direct photolysis; however, the mass balance and yields of the products are substantially decreased, as shown in Table 1.

Table 1. Conversion and Product Yields of the Photochemical Reaction of 1 Sensitized by Triplet Sensitizers Xanthone and Acetophenone

sensitizer	conv., %[a]	ED1P, %	ED1Pb, %	ED1Pc, %[b]	M.B., %[c]
none	15	24	29	26:9	90
X[d]	76	2	2	18:1.5	15
AP[e]	83	3	8	3:0	21

[a] Conversion of **1**. [b] Yields given correspond to percent **1Pc** (cis): percent **1Pc** (trans). [c] Mass balance. [d] Xanthone. [e] Acetophenone.

Scheme 3



Photolysis of enediyne **2** in 2-propanol, interestingly, yields the cyclized **2P** as the only product observed by GC characterization with high mass balance (ca. 75%; Scheme 3); reduced products such as those observed from photoreaction of **1** are not formed to any detectable extent. In the presence of 1,4-cyclohexadiene, however, although photochemical conversion of the enediyne does take place, no product is observed by GC, suggesting the formation of an uncharacterized polymeric material. In the case of triplet sensitization of **2** by excitation and subsequent energy transfer from xanthone, no conversion of the enediyne is observed.

In the laser flash photolysis experiments, excitation of a deaerated solution of **1** in hexane leads to the production of a single transient with a maximum at ca. 320 nm, shown in Figure 1, which decays with a lifetime of $t \sim 20$ ms. The decay,

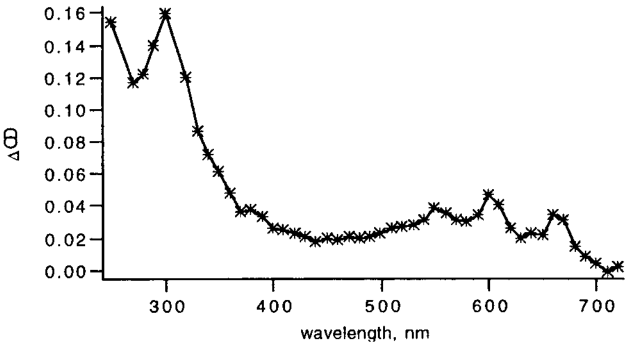


Figure 1. Transient absorption spectrum of **1** in hexane, about 500 ns after the laser pulse.

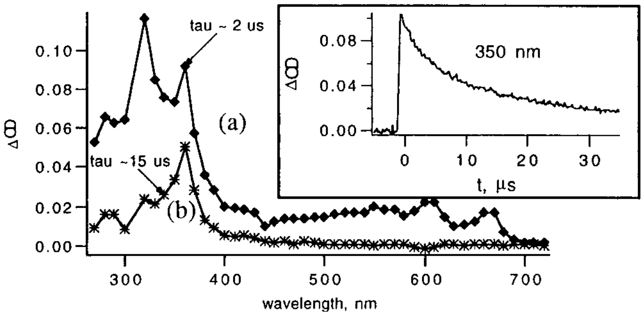


Figure 2. Transient absorption spectra of **1** in 2-propanol immediatly after the laser pulse (a) and approximately 10 μs after the pulse (b). The decay of **1** at 350 nm is shown in the inset.

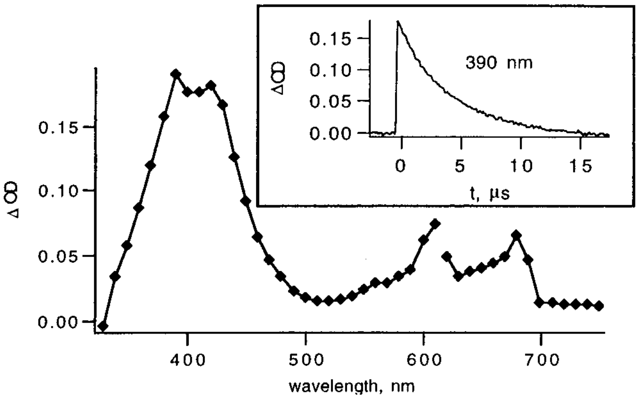


Figure 3. Transient absorption spectrum of **3** in acetonitrile approximately 500 ns after the laser pulse. The decay of **3** at 390 nm is shown in the inset.

monitored at 320 nm, is quenched by molecular oxygen with a rate constant of 1.3 × 10^9 M^{-1} s^{-1}. The transient spectrum of **1** in 2-propanol, however, in which the enediyne is reactive, contains an additional absorption band in the region of 370 nm, which decays with a much longer lifetime, as evidenced by observation at ~15 ms after the laser pulse (Figure 2). A similar transient is obtained when **1** is photolyzed in hexane in the presence of 1,4-cyclohexadiene in which the enediyne is reactive, as mentioned before. Furthermore, **1** quenches the excited-state triplet transient of xanthone, with a rate constant of 9 × 10^9 M^{-1} s^{-1}.

Flash photolysis of **2** yields a single transient species (Figure 3), which does not exhibit the solvent dependence of **1**. This species has an absorption spectrum similar in structure to that of **1** in hexane, as shown in Figure 3, with the maximum red shifted to approximately 390 nm. Monitoring the decay of the transient in acetonitrile yields a lifetime of ~35 ms; in 2-propanol, this lifetime is reduced to 15 ms. As observed for the transient of **1**, the transient of **2** is also quenched by molecular oxygen, with a rate constant of 1 × 10^9 M^{-1} s^{-1}. Again, **2** is an effective quencher of the triplet transient of xanthone; the decay of the latter, monitored at 635 nm, is quenched by **2** with a rate constant of ~5 × 10^9 M^{-1} s^{-1}, while a concurrent growth is observed at 370 nm, near the maximum of the transient of **2**.

Discussion

The photolysis studies described in the Results section provide proof that the enediynes **1** and **2** can react photochemically to produce the same cyclized product that would be formed if a thermal Bergman rearrangement were to take place. The questions which arise pertain to the mechanism of the reaction; in particular: (i) What is the intermediate(s) responsible for the formation of the cyclized products, and how does the mechanism compare to that of the thermal case? (ii) What is the mechanism that leads to the formation of the photoreduced products and why are the latter produced only from **1**? (iii) Are the transients observed by laser flash photolysis present on the photoreaction pathway of the enediynes, and what is their nature? We will attempt to answer these questions by looking at the data obtained from both steady-state and time-resolved experiments and by referring to similar systems which have been extensively covered in the literature.

A priori there are a number of different possible mechanisms which could plausibly account for the formation of the products observed. These include the intermediacy of either radical, ionic, or radical ionic intermediates, and could entail either a concerted or a stepwise mechanistic pathway. On the basis of this assumption, one can write out a multitude of mechanistic schemes which would lead to the formed products. Furthermore, it is also possible that the cyclized products observed could result from secondary processes, whereupon a stable product absorbs a second photon to further rearrange to the observed compounds, although in this study such a mechanism would be highly unlikely, since isolation and subsequent photolysis of the primary photoproducts do not react further to the cyclized material.

A single step concerted mechanism to yield an intermediate that would then undergo hydrogen abstraction fails to account for the different types of products observed for **1**, since clearly **1Pa** arises from a cyclization step that is absent in the pathway to **1Pb** and **1Pc**. An ionic mechanism is considered unlikely, mainly due to the reactivity of the enediynes in nonprotic media such as 1,4-cyclohexadiene, which acts as a hydrogen donor. Moreover, if the reaction were to be of ionic nature, one would expect an isopropoxy adduct from photolysis of **1** in 2-propanol; instead, the α-isopropyl adduct **1Pb** is formed. Hence it is much more likely that a radical mechanism is at play, at least in the formation of the acetylene reduction products **1Pb** and **1Pc**. There is, additionally, a precedence for radical reactivity of acetylenes.[26] *tert*-Butylphenylacetylene, for example, when photolyzed in 2-propanol, has been shown to produce the respective cis and trans alkene from two hydrogen abstraction steps, as well as the alkene formed by addition of an equivalent of 2-propanol across the triple bond, just as has been observed for photoreaction of **1** yielding cis and trans **1Pc** and **1Pb**, respectively.

As far as the formation of an intermediate involved in the production of the cyclized products **1Pa** and **2P**, there are two plausible scenarios, based on the time-resolved data obtained

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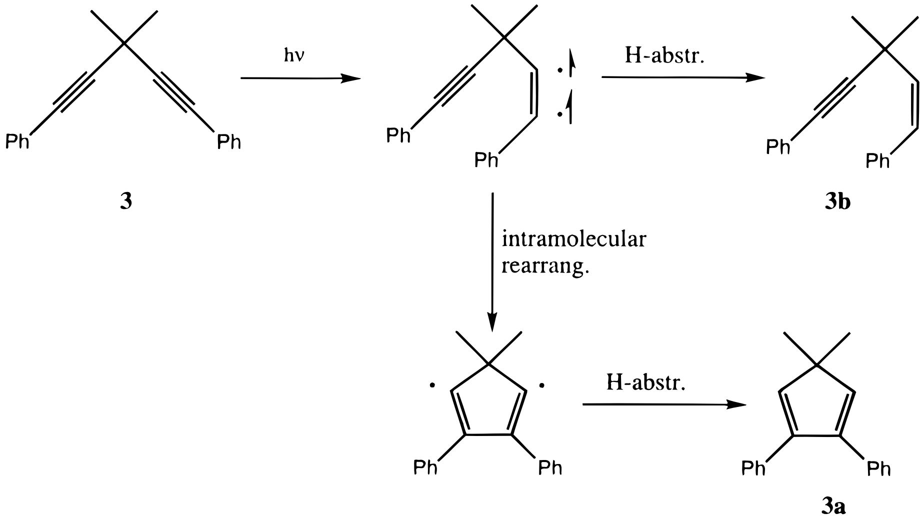
[26] Perreten, J.; Chihal, D. M.; Griffin, G. W.; Bhacca, N. S. *J. Org. Chem.* **1976**, *41*, 3931.

Scheme 4



in this study and on literature precedents of similar systems. The first involves the intermediacy of a radical cation species. In fact, it has been reported that photolysis of **2** in the presence of suitable electron acceptors leads to the production of substituted indene compounds via an enediyne-derived radical cation.[25] Moreover, extensive literature exists on the absorption spectra of aromatic radical cations formed by direct excitation;[27,28] these spectra are structurally very similar to the ones obtained for **1** and **2**, particularly in terms of the visible absorption band. This scenario, however, seems to be rather unlikely under the conditions of the system studied herein. The reaction of the enediynes to yield the cyclized substituted naphthalenes proceeds under steady-state conditions without the presence of electron acceptors, and clearly the naphthalene products observed for both **1** and **2** are structurally different from the indenes produced in the aforementioned study. Furthermore, if the transient spectra of **1** and **2** were to reflect the presence of a radical cation, then one would expect to observe a particular behavior characteristic of such species, such as quenching of the decays by nucleophiles such as acetate or amines,[29,30] and lifetime elongation through addition of electron traps such as carbon tetrachloride. Although we attempted to quench the transient decays of **1** and **2** with a variety of amines including DABCO, triethylamine, and *n*-butylamine, as well as acetate, and we added various concentrations of carbon tetrachloride, we did not observe in any one case any significant quenching or lifetime elongation, respectively. Moreover, the transients were efficiently quenched by oxygen at close to the diffusion-controlled limit, which would not be expected if the transient were attributed to a radical cation.[29]

A second scenario would entail the formation of a radical species that would lead to the cyclized naphthyl products. Enynes[31, 32] and diynes,[33−35] structural relatives of the compounds described herein, have been shown to undergo cyclization reactions via radical intermediates, from both the excited-state singlet and triplet states. Additionally, the presence of a radical transient would explain the hydrogen abstraction steps during photolysis of the enediynes and would justify the observed quenching of the transient decay by oxygen.

It is worthwhile, at this point, to consider the photoreactivity of the diyne **3**, studied by Zimmerman and co-workers,[34] which possesses a striking similarity to the photoreactivity of **1**. In particular, photolysis of **3** in 2-propanol produced the reduced **3b** and the cyclopentadiene **3a**. The mechanism postulated by Zimmerman involved excitation of one triple bond in the excited triplet state, which then could either be reduced by two consecutive hydrogen abstraction steps from two individual 2-propanol molecules or, alternatively, could cyclize to yield a 1,4-cyclopentadienyl biradical, which would then abstract hydrogens to produce **3a** (Scheme 4). At first glance, comparison of the products obtained from **1** to those from **3** would suggest that the underlying mechanism should be similar for both systems. There are, however, the following differences which need to be considered: (i) whereas **1** does display similar reactivity to **3**, **3** produces only the cyclized material and no photoreduction products; and (ii) triplet sensitization of **3** with xanthone produces **3a** and **3b** in roughly the same ratio as direct photolysis of **3**, whereas in the case of triplet sensitization of **1** the ratio of the photoreduction products **1Pb** and **1Pc** to cyclized product **1Pa** is much larger than that obtained during direct irradiation—furthermore, triplet sensitization of **2** yields to no product formation.

To account for these differences, we turn to a qualitative argument relating the structures of the observed enediynes to the expected excited state responsible for their reaction. The quantum yield of fluorescence for a given aromatic molecule can be correlated to its structural rigidity; we expect the phenyl substituents on the triple bonds of **2** to force the molecule into a more rigid conformation than **1**;[36] this hypothesis is supported by the significantly larger fluorescence quantum yield of **2** compared to that of **1**. A lower fluorescence quantum yield

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[27] Liu, A.-D.; Sauer, M. C.; Jonah, C. D.; Trifunac, A. D. *J. Phys. Chem.* **1992**, *96*, 9293−9298.

[28] Liu, A.; Sauer, M. C.; Loffredo, D. M.; Trifunac, A. D. *J. Photochem. Photobiol.* **1992**, *67*, 197−208.

[29] Johnston, L. J.; Schepp, N. P. *J. Am. Chem. Soc.* **1993**, *115*, 6564−6571.

[30] Workentin, M. S.; Johnston, L. J.; Wayner, D. D. M.; Parker, V. D. *J. Am. Chem. Soc.* **1994**, *116*, 8279−8287.

[31] Tinnemans, A. H. A.; Laarhoven, W. H. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1111.

[32] Zheng, M.; DiRico, K. J.; Kirchhoff, M. M.; Phillips, K. M.; Cuff, L. M.; Johnson, R. P. *J. Am. Chem. Soc.* **1993**, *115*, 12167−12168.

[33] Johnson, R. P. *Chem. Rev. (Washington, D.C.)* **1989**, *89*, 1111−1124 and references therein.

[34] Zimmerman, H. E.; Pincock, J. A. *J. Am. Chem. Soc.* **1973**, *95*, 3246.

[35] Hayashi, T.; Mataga, N.; Inoue, T.; Kaneda, T.; Irie, M.; Misumi, S. *J. Am. Chem. Soc.* **1977**, *99*, 523.

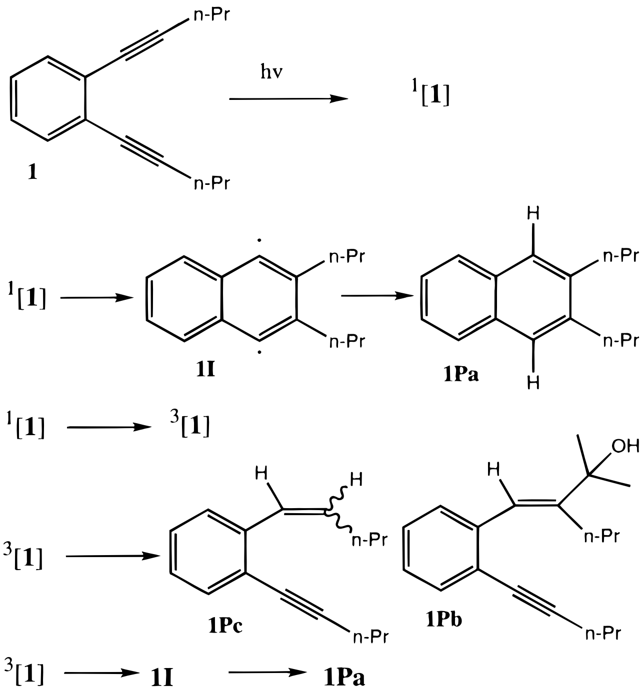
[36] Turro, N. J. *Modern Molecular Photochemistry*; The Benjamin/Cummings Publishing Co., Inc.: Menlo Park, CA, 1978; Chapter 5, p 111 and Chapter 6, p 171.

would, in turn, imply that the probability is greater of other processes for deactivation of the excited singlet state taking place, such as intersystem crossing to the triplet state or reactions from the singlet state. If we were to assume that the photoreduction products **1Pb** and **1Pc** arise from the triplet state whereas the cyclized **1Pa** arises from the singlet excited state, this would explain why **2** does not form the equivalent photoreduction products, if its intersystem crossing efficiency is lower than that of **1**.

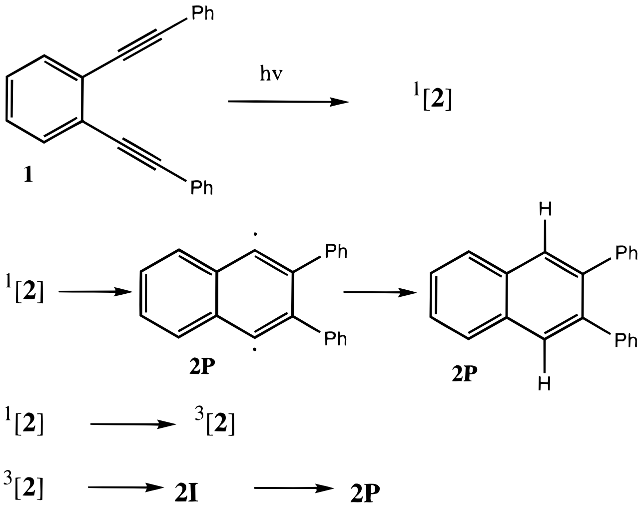
The involvement of two separate excited states in the formation of the two classes of products can be further justified by the behavior of the transients produced by photolysis of the two enediynes **1** and **2**. In particular, **1** produces an additional transient absorption band that is lacking in the spectrum derived from **2.** Taking the fact that **1** also produces under photolysis conditions the photoreduction products which are lacking in the reaction of **2**, the common spectrum to the radical intermediate leading to **1Pa** and **2P** may be correlated with the transient unique to **1** to the products **1Pb** and **1Pc**. The time-resolved triplet sensitization experiments would then suggest that the radical leading to the Bergman-type product could also be formed from the triplet state, although during direct excitation the electronic state most probably involved would be the excited singlet state.

It remains to elucidate the structure of the radical intermediate leading to formation of **1Pa** and **2P**. Since the cyclized Bergman-type product and the uncyclized photoreduction products for the reaction of **1** seem to be produced from two distinct transients, it is very likely that the former transient observed be formed after the cyclization step, structurally resembling the inert product; the most possible structures would then be either a 1-naphthyl radical or a 1,4-naphthyl biradical. Both aromatic radicals[38] and biradicals[37] have been investigated in a time-resolved fashion in the literature. Specifically, the study of the 9,10-anthracenyl biradical reported by Schottelius et al.[37] may be pertinent to our system. Although the absorption bands of the transient spectrum of the latter species differs from that observed for **1** and **2**, specifically in lacking the visible absorption band, the calculated rate constants for hydrogen abstraction reactions are very similar. In particular, Schottelius reports bimolecular rates of hydrogen abstraction from acetonitrile and 2-propanol to be 1.1×10^3 and 6.5×10^3 M^{-1} s^{-1}, respectively. From the decay lifetimes of the transient of **2** we obtain pseudo-first-order rate constants of 7×10^4 and 3×10^4 M^{-1} s^{-1} for those two solvents; adjusting for the molarity of the solvents, which are 19 and 13 M for acetonitrile and 2-propanol, respectively, we arrive at bimolecular rate constants of 2 and 4×10^3 M^{-1} s^{-1}. These estimations would actually correspond to upper limits of the hydrogen abstraction rate, since they assume that all molecules of **2** react by hydrogen abstraction, whereas it is highly probable that a portion of **2** reacts intermolecularly with itself. Furthermore, not only do these values fall close to those calculated for the anthracenyl biradical, but they are also much lower than rates of hydrogen abstraction reported for aromatic monoradicals.[38]

Scheme 5



Scheme 6



We propose the most probable mechanism taking place during photoreaction of **1** and **2** as shown in Schemes 5 and 6, respectively. Both enediynes are photochemically excited to the singlet state. Reaction from the singlet state leads to formation of the Bergman-type cyclized products, most probably via a naphthyl biradical, which abstracts two hydrogens from an isopropyl molecule to yield the final **1Pa** and **2P**. The excited **1** can undergo intersystem crossing to the triplet state, which is responsible for the acetylene photoreduction products observed. It is also possible that the triplet state of the enediynes can also produce the cyclized products **1Pa** and **2P**, as indicated in the last equation of each scheme.

Before closing, let us comment on the observed effect of the structure of the enediynes as related to their reactivity,[39] specifically the effect of the triple bond substituents on the product formation of the enediynes. Comparison of the product distribution of **1** and **2** indicates that the presence of aromatic rings on the triple bonds drives the reaction toward cyclization and eliminates the formation of photoreduction products. This may be correlated to the hypothesized intersystem crossing efficiency of the two subsets; in particular, as mentioned before, the phenyl substituents on **2** may cause increased rigidity in the overall structure through steric hindrance or even possibly some π-stacking interactions, absent in **1**, which would lead to a less efficient triplet state crossing from the singlet. Assuming that the singlet state is responsible for the production of the

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[37] Schottelius, M. J.; Chen, P. *J. Am. Chem. Soc.* **1996**, *118*, 4896–4903.

[38] Scaiano, J. C.; Stewart, L. C. *J. Am. Chem. Soc.* **1983**, *105*, 3609–3613.

naphthyl products but not the photoreduction products, one would expect the latter to be formed mainly in the triplet photoreaction of **1**.

Conclusions

We report the photosensitized reaction of a series of enediynes which yield a cyclization product identical to that which would be expected from a thermal Bergman rearrangement. Both steady-state and time-resolved investigations strongly suggest that the cyclized products obtained for each of the enediyne analogues are formed via a mechanism that produces a 1,4-naphthyl biradical as its intermediate. The photochemical reaction differs from a thermal analogue mainly in that the former seems to arise as a result of excitation of an acetylenic unit rather than of a conjugative effect of the entire enediyne functionality.

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(39) Photolysis of the compounds 1,2-bis(1-pentynyl)cyclopentene (**3**) and 1,2-bis(1-phenylacetylenyl)cyclopentene (**4**) under the same conditions as those reported for **1** and **2** yielded a similar product distribution, specifically 5,6-dipropylindan and 1-(1-pentenyl)-2-(1-pentynyl)cyclopentene for **3** and 5,6-diphenylindan for **4** (preliminary results). Although the same reactivity trends are observed for these compounds, with the phenyl subsituted **4** being more reactive than **3**, the overall product yields of **1** and **2**, whose double bond is part of an aromatic framework, are much higher than those for **3** and **4**, where the double bond is isolated in a cyclopentenyl ring. In the latter set, the orbitals of the double bond would be conjugated only with the triple bonds on either side, whereas in the former set there would be a competing conjugative effect with the aromatic framework of the phenyl ring in which it is contained. This observation would suggest that the photoreactivity of the enediyne compounds studied is a result of excitation of the individual acetylenic units and does not rely on a conjugative effect of the enediyne functionality.