C1−C5 Photochemical Cyclization of Enediynes

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The high biological activity of the naturally occurring enediyne antibiotics such as calicheamicin, esperamicin, dynemicin, and neocarzinostatin[1] is associated with formation of a reactive 1,4-dehydrobenzene diradical through a thermal cyclization of the enediyne moiety (the Bergman cyclization).[2] The simultaneous formation of *two* radical centers is important because it leads to the abstraction of two hydrogen atoms, one from the sugar backbone of each strand of a double-stranded DNA. The double hydrogen-atom (H-atom) abstraction results in double-strand cleavage of DNA and, ultimately, the self-programmed cell death (apoptosis).

Unfortunately, the high reactivity of natural enediynes renders them extremely toxic. This explains recent efforts devoted to the development of the photochemical version of the Bergman cyclization[3,4] as an attractive strategy for designing less toxic enediyne drugs. The appeal of the photochemical activation is that it allows time- and space-resolved drug activation with the drug being harmless until activated with light. Notwithstanding several promising results, efficient photochemical double-strand DNA cleavage is still a challenge due to the low efficiency of H-atom abstraction by the reactive species.

This study reports a new photochemical cyclization of tetrafluoropyridinyl (TFP)-substituted enediynes that is accompanied with *four* H-atom abstractions from organic substrates and is mechanistically different from the Bergman cyclization.

The TFP-substituted enediynes **2** were readily prepared using a one-pot deprotection−nucleophilic coupling methodology (developed by one of us)[5] from the corresponding 1,2-bis(trimethylsilylethynyl)benzenes **1** obtained in a straightforward two-step synthesis from commercially available anthranilic acids or *o*-xylene (Scheme 1).

Upon UV irradiation (320 nm) in the presence of 1,4-cyclohexadiene in acetonitrile, the bis-TFP enediynes undergo photochemical transformation into a mixture of isomeric indenes **3** and **4** (Scheme 2).[6] The reaction is regioselective, and in the case of a nonsymmetrically substituted enediyne **2c**, one of the isomers is formed preferentially (e.g., when X = H, Y = Cl, the ratio of **3c**/**3c′** is ca. 9/1) (see Figure 1). The observed reaction products suggest 5-*exo*-dig C1−C5 cyclization with formation of a fulvene intermediate **5**, which is too reactive to be isolated under the reaction conditions and undergoes further reduction (vide infra).[7]

The formation of such an intermediate is remarkable in the context of the recent prediction by Schreiner et al.[8] who reported that on the basis of BLYP/6-31G** computations the 5-exo-dig cyclization of (Z)-hex-3-ene-1,5-diyne to the corresponding fulvene diradical should be 39 kcal/mol endothermic. Such high endothermicity is not surprising because, unlike in the Bergman cyclization, the product is not stabilized by aromaticity. Taking into account the estimated cyclization barrier of 42 kcal/mol, the fulvene diradical
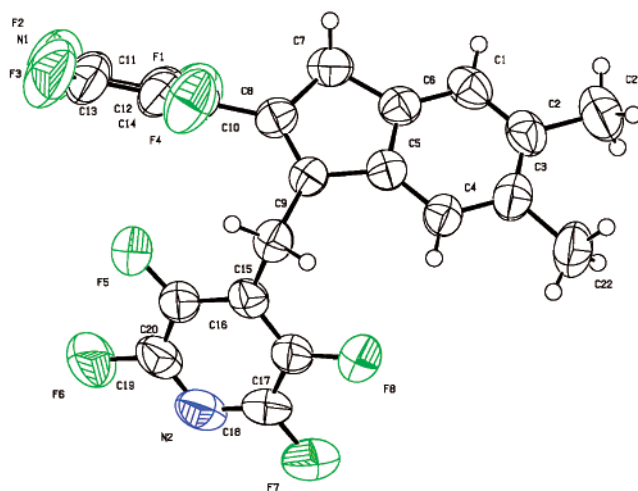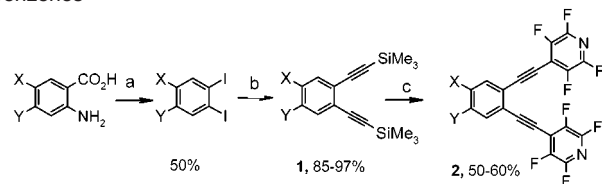
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Figure 1. ORTEP plot of indene **3b**. Thermal ellipsoids are shown at the 50% probability level.

Scheme 1. Synthesis of 1,2-Bis(tetrafluoropyridinylethynyl)Benzenes

Scheme 2. Novel C1−C5 Photochemical Cyclization of 1,2-Bis(tetrafluoropyridine) Enediynes

|	**3**	**4**
a, X=Y=H	22%	traces
b, X=Y=Me	17%	traces
c, X=Cl, Y=H	18%	3%
c′, X=H, Y=Cl	2 %	<1%
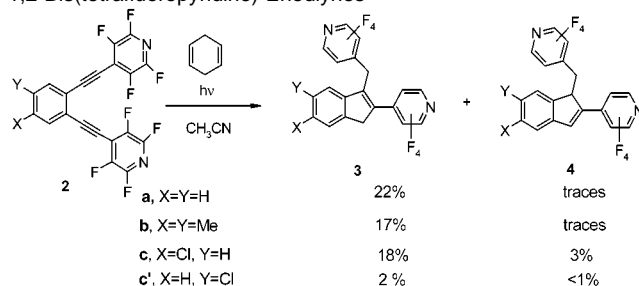
should reopen to give the starting enediyne rather than abstract a hydrogen atom.

Another surprising feature of the new photochemical process is that bis-TFP enediynes which are much more reactive than the bis-(phenyl)-substituted analogues under the above conditions, do not undergo the photochemical transformation in isopropyl alcohol, the solvent that has been reported to be the most efficient hydrogen atom donor for the photochemical Bergman cyclization of bis-(phenyl) enediynes.[4]
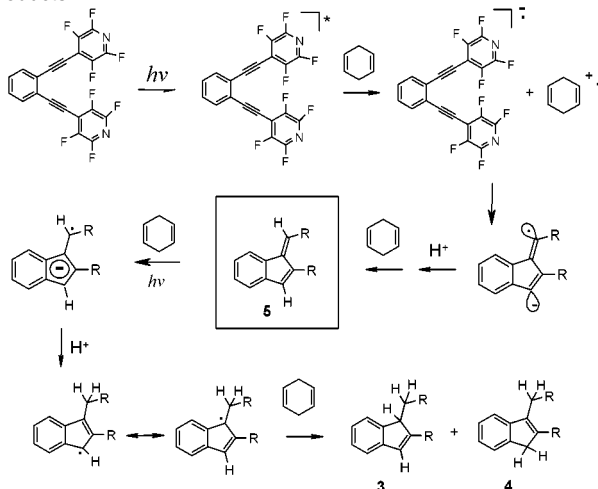
These peculiar features can be explained by the fact that the presence of strongly electron-withdrawing TFP substituents renders

Scheme 3. Comparison of Diradical and Radical Anion Pathways for the C1−C5 Cyclization of Parent Enediyne
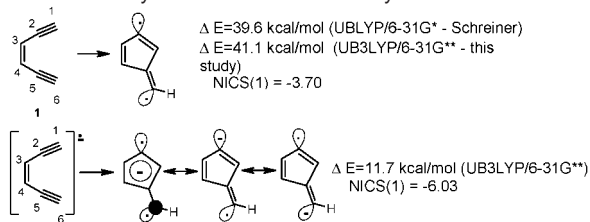
Scheme 4. Possible Scheme for Formation of the Photochemical Products

photoinduced electron transfer (PET) from 1,4-cyclohexadiene to the singlet excited states of the enediynes **2a**−**c** highly exothermic (>25 kcal/mol). At this exothermicity, PET should be diffusion-controlled and we do observe efficient quenching of fluorescence of enediyne **3a** by cyclohexadiene.[9] Unlike the cyclization of neutral enediynes, the C1−C5 cyclization of the enediyne radical anions leads to an intermediate stabilized through resonance involving cyclopentadienyl anion (Scheme 3), thus rendering this cyclization mode possible.[10]

Taking into account the circumstantial evidence for the radical anion pathway, we performed the photolysis in the presence of CH₃-OD and observed partial deuterium incorporation at both methylene groups of indene **3a**.

These observations suggest that C1−C5 ring closure with the formation of a fulvene radical anion is initiated by electron transfer from 1,4-cyclohexadiene to the enediyne excited singlet state. The fulvene radical anion may either abstract a hydrogen atom from 1,4-cyclohexadiene or abstract a proton from the cyclohexadienyl radical cation. Both pathways have precedents: hydrogen donor activity of 1,4-cyclohexadiene is commonly used for quenching of 1,4-diradicals formed in Bergman cyclizations, whereas radical cations are known to be very strong acids (e.g., pK_a of toluene radical cation in DMSO is −20).[11] The relative timing and regioselectivity of proton and H-atom abstraction are not clear at this time. Although the protonation is likely to be fast, the possibility of a H-atom abstraction in an intimate ion pair cannot be eliminated. A possible sequence of further steps accounting for the formation of the observed products is outlined in Scheme 4.

To summarize, we have found a new mechanistically interesting C1−C5 cyclization of enediynes. Unlike the Bergman cycloaromatization pathway, which involves two H-atom abstractions, the new reaction is accompanied by four formal H-atom abstractions (or two H-atom/two proton abstractions) and thus may provide a new DNA-damaging warhead for use in biochemical applications.[12]

A key feature of the new reaction is the likely involvement of photoinduced electron transfer (PET) from an organic donor to the excited enediyne. Further mechanistic studies, solvent, isotope, and substituent effect studies as well as the application of this novel reaction to DNA cleavage will be reported in a due course.

Supporting Information Available: Experimental procedures, ¹H, ¹³C, ¹⁹F NMR spectra for all compounds, details of B3LYP/6-31G** computations (PDF). An X-ray crystallographic file of indene **3b** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Indenes **3a**−**c** and **4c** were isolated by HPLC and completely characterized by spectral methods and, in the case of **3b**, by X-ray crystallography (See the Supporting Information for the details and Figure 1 for the X-ray structure). Products of radical addition to cyclohexadiene are also present in the reaction mixture as confirmed by GC−MS. The overall reaction mass balance is high, but the isomeric reaction products are hard to separate. This accounts for the low isolated product yields.

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