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 neocarzinostatin1 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 cyclization3,4 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(trimethylsilyl-ethynyl)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 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...
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. 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– the singlet excited states of the enediynes 2a 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.

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Supporting Information Available: Experimental Procedure, 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.

References


(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.

(7) Fulvenes are easily reduced: Tacke, M.; Fox, S.; Cuffe, L.; Dunne, J. P.; Rehm, D.; Weller, A. Isr. J. Chem. 1970, 8, 59. $\Delta c_{\text{rev}} = f(\text{Fe}^{3+}/\text{Fe}^{2+} - \text{e}_2^{\text{vis}} - \epsilon)$ where the Coulombic attraction term $\text{Fe}^{3+}/\text{Fe}^{2+}$ is estimated as 1.3 kcal mol $^{-1}$ (see Mangion, D.; Kendall, J.; Aragundi D. R. J. Org. Lett. 2001, 3, 45). Oxidation potential of 1,4-cyclohexadiene in CH2CN was taken as 1.74 (Shono, T.; Ikeda, A.; Hayashi, J.; Hakozaki, S. J. Am. Chem. Soc. 1975, 97, 4261).

(8) The importance of the aromatic resonance in Scheme 3 is supported by nuclear independent chemical shift (NICS) calculations that show increased aromatic ring current in this radical anion and by natural bond orbital analysis of its electronic structure. Benzenannellation and benzylic conjugation with terminal aliphatic system are likely to decrease the activation energy further and make this reaction exothermic. Alabugin, I. V.; Manoharan, M. Manuscript in preparation.


(10) Potentially, such warheads can target either DNA sugar residues or nucleobases (e.g., guanine). Armitage, B. Chem. Rev. 1998, 98, 1171. JA026630D