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Theoretical Study of the Bergman Cyclization of 2,3-Diethynyl-1-nitrotropylium Ion: Formation of a Nitroxide Radical Amenable to EPR Detection for Biological Applications.

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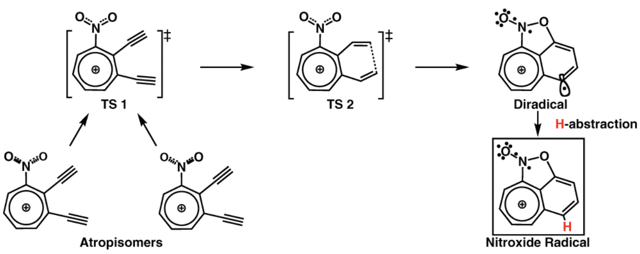
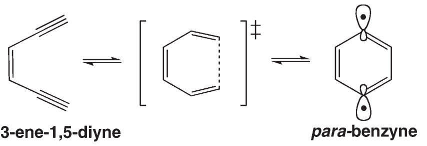


We report a DFT study of a Bergman cyclization producing a stable triplet nitroxide diradical and monoradical (after H abstraction from an external source). The monoradical is predicted to be amenable to detection by EPR methods to potentially probe the structure and dynamics of enediyne molecules for drug interactions.

The Bergman cyclization,[1] a pericyclic reaction[2] that yields a *p*-benzyne diradical,[3] has garnered much attention because it underlies the antitumor action of natural enediynes.[4] Since its discovery, the Bergman cyclization has advanced many fields of endeavor, such as mechanistic organic chemistry,[5] material science,[6,7] and drug discovery[8] and provided a unique opportunity for testing the accuracy of computational methods.[9] However, no Bergman cyclization has yet yielded directly an EPR-detectable nitroxide radical.[10]



Herein, we present a computational study of a Bergman cyclization that produces a triplet nitroxide diradical **$\mathbf{1P_T}$** and monoradical **$\mathbf{1P_T{-}H}$** (after H abstraction); the latter is predicted to be amenable to detection by EPR methods experimentally (Scheme 1). The impetus was to develop a spin-labeled molecule[11] coupled with the Bergman cyclization. The study was done at the uB3LYP/6-31G** level of theory,[12] which is known to well reproduce experimental values of the bond distances and bond angles for the gas-phase structure of (*Z*)-3-ene-1,5-diyne[13] and the energetics corresponding to its Bergman cyclization.[14,15]

One of the unpaired electrons from the triplet diradical **$\mathbf{1P_T}$** is localized at C11 (Scheme 1). The second unpaired electron, at N, is involved in three-electron interactions with the lone-pair electrons at O2. **$\mathbf{1P_T}$** is highly stabilized relative to its precursors **1A** and **1B** by 50.2 kcal/mol (Figure 1), which is very unique to this particular Bergman cyclization. Since through-bond coupling and interactions between the unpaired electrons are not possible in triplet diradicals, an unpaired electron localized in the $p_{\text{in-plane}}$ orbital at C11 in **$\mathbf{1P_T}$** is expected to be as reactive toward intermolecular hydrogen abstraction as would a phenyl-type radical.[9] Hydrogen abstraction by **$\mathbf{1P_T}$** from any available source yields the triplet radical **$\mathbf{1P_T{-}H}$**.

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(1) (a) Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660–661. (b) Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25–31.

(2) (a) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Academic Press: New York, 1970. (b) Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, *87*, 395–397.

(3) Borden, W. T., Ed. *Diradicals*: John Wiley & Sons, Inc.: New York, 1982.

(4) For leading reviews, see: (a) Wenk, H. H.; Winkler, M.; Sander, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 502–528. (b) Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed.* **1991**, *30*, 1387–1530. and references therein.

(5) (a) Vavilala, C.; Byrne, N.; Kraml, C. M.; Ho, D. M.; Pascal, R. A., Jr. *J. Am. Chem. Soc.* **2008**, *130*, 13549–13551. (b) Alabugin, I. V.; Breiner, B.; Manoharan, M. *Adv. Phys. Org. Chem.* **2007**, *42*, 1–33. (c) Zeidan, T.; Kovalenko, S. V.; Manoharan, M.; Alabugin, I. V. *J. Org. Chem.* **2006**, *71*, 962–975. (d) Alabugin, I. V.; Manoharan, M.; Kovalenko, S. V. *Org. Lett.* **2002**, *4*, 1119–1122. (e) Jones, G. B.; Warner, P. M. *J. Am. Chem. Soc.* **2001**, *123*, 2134–2145. (f) Prall, M.; Wittkopp, A.; Fokin, A.; Schreiner, P. R. *J. Comput. Chem.* **2001**, *22*, 1605–1614.

(6) (a) Chen, X.; Tolbert, L. M.; Hess, D. W.; Henderson, C. *Macromolecules* **2001**, *34*, 4104–4108. (b) Shah, H. V.; Babb, D. A.; Smith, D. W., Jr. *Polymer* **2000**, *41*, 4415–4422. (c) John, J. A.; Tour, J. M. *J. Am. Chem. Soc.* **1994**, *116*, 5011–5012.

(7) Bowles, D. M.; Palmer, G. J.; Landis, C. A.; Scott, J. L.; Anthony, J. E. *Tetrahedron* **2001**, *57*, 3753–3760. (b) Bowles, D. M.; Anthony, J. E. *Org. Lett.* **2000**, *2*, 85–87.

(8) Galm, U.; Hager, M. H.; Van Lanen, S. G.; Ju, J.; Thorson, J. S.; Shen, B. *Chem. Rev.* **2005**, *105*, 739–758. and references cited within.

(9) (a) Wang, E. B.; Parish, C. A.; Lischka, H. *J. Chem. Phys.* **2008**, *129*, 044306(1−8). (b) Kraka, E.; Cremer, D. *J. Am. Chem. Soc.* **2000**, *122*, 8245–8264. (c) Cramer, C. J. *J. Am. Chem. Soc.* **1998**, *120*, 6261–6269. (d) Schreiner, P. R. *J. Am. Chem. Soc.* **1998**, *120*, 4184–4190.

(10) (a) Usuki, T.; Inoue, M.; Akiyama, K.; Hirama, M. *Bioorg. Med. Chem.* **2005**, *13*, 5218–5224. (b) Usuki, T.; Mita, T.; Lear, M. J.; Das, P.; Yoshimura, F.; Inoue, M.; Hirama, M.; Akiyama, K.; Tero-Kubota, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5249–5253. (c) Wisniewski Grissom, J.; Gunawardena, G. U. *Tetrahedron Lett.* **1995**, *36*, 4951–4954.

(11) Rajca, A.; Takahashi, M.; Pink, M.; Spagnol, G.; Rajca, S. *J. Am. Chem. Soc.* **2007**, *129*, 10159–10170. and references cited within.

(12) All calculations presented in the paper were carried out at uB3LYP/6-31G** with Gaussian 03 at the default temperature of 298.15 K. See the Supporting Information for more details, including references and results obtained with uBLYP/6-31G**.

(13) McMahon, R. J.; Halter, R. J.; Fimmen, R. L.; Wilson, R. J.; Peebles, S. A.; Kuczkowski, R. L.; Stanton, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 939–949.

(14) For experimental values of the enthalpies corresponding to the Bergman cyclization, see: Roth, W. R.; Hopf, H.; Horn, C. *Chem. Ber.* **1994**, *127*, 1765–1769.

(15) See the Supporting Information for additional details and results of control calculations with unrestricted B3LYP and BLYP methods in combination with 6-31G** and 6-311+G** basis sets and a discussion of the relevant literature.

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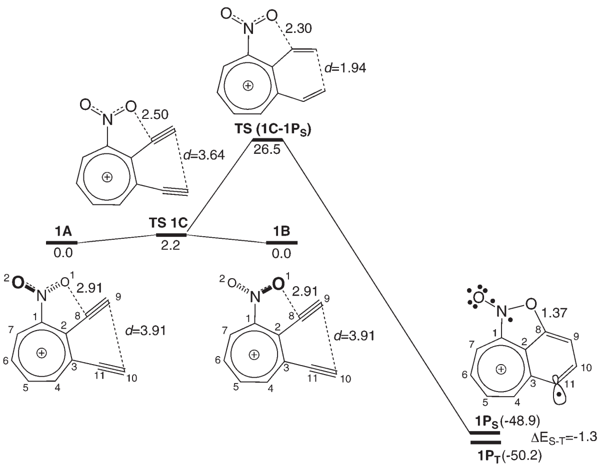
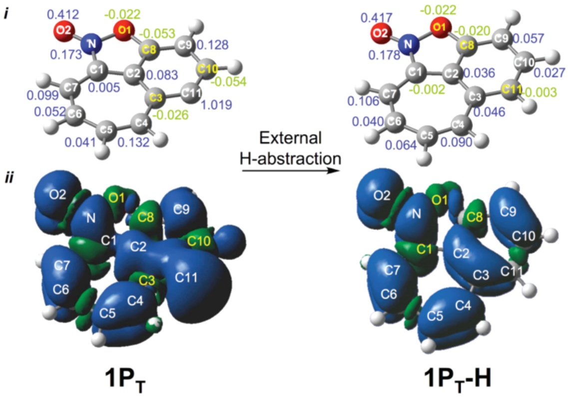


FIGURE 1. PES corresponding to the Bergman cyclization of **1A** and **1B** calculated at uB3LYP/6-31G**. Enthalpy values and $\Delta E_{S-T,\ \mathrm{adiabatic}}$ (include ZPE) are given in kcal/mol; reported bond distances correspond to the species in their singlet (S) state are given in Å.

SCHEME 1. Optimized, Spin-Labeled Triplet Diradical 1P$_{\mathrm{T}}$ and Radical 1P$_{\mathrm{T}}$−H and Their Spin Densities at uB3LYP/6-31G Level of Theory**[a]



[a] Values of positive and negative spin densities are represented by blue and green numbers (*i*) and lobes (*ii*), respectively.

The nitroxide moieties of **1P$_{\mathrm{T}}$** and **1P$_{\mathrm{T}}$−H** are coplanar with the fused aromatic rings, which facilitate the delocalization of the spin density. The DFT calculations show that the spin density is delocalized from p_π N−O(2) in **1P$_{\mathrm{T}}$** and **1P$_{\mathrm{T}}$−H**. The spin density of 1.019 on C11 indicates that the unpaired electron does not contribute efficiently to the spin density of the aromatic system, as would be expected.

Potential Energy Surface. Figure 1 shows the potential energy surface (PES) of the Bergman cyclization yielding **1P$_{\mathrm{T}}$**. Diradical **1P$_{\mathrm{T}}$** is obtained from **1A** and **1B**. In **1A** and **1B**, the tropylium ion is substituted vicinally with respect to acetylenic group C(8)≡C(9)H by the nitro group NO_2. Alabugin et al. studied the substituent effect of the nitro group in the ortho position on benzannelated enediynes and showed a modest decrease in energy relative to (*Z*)-3-ene-1,5-diyne[13] through the steric repulsion between the NO_2 group and the vicinal acetylenic terminus.[5b,c] In our study, we replaced the benzene ring with the tropylium ion. The seven-membered ring of the tropylium ion is flat as is benzene's six-membered ring, similar to tropone and tropolone natural products due to their tropylium ion cores.[16] We do not believe the positive charge of the tropylium ion system plays a significant role in the cyclization process on the basis of calculations on the corresponding anionic system **4** (a planar triplet state cycloheptatrienyl anion),[17] vide infra. Compounds such as **1A** and **1B** could be synthesized from tropylium ion salt, for example, commercially available tropylium ion tetrafluoroborate, $C_7H_7^+\cdot BF_4^-$, which has reasonable thermodynamic stability.[18] However, our calculations did not include the BF_4^- counterion.

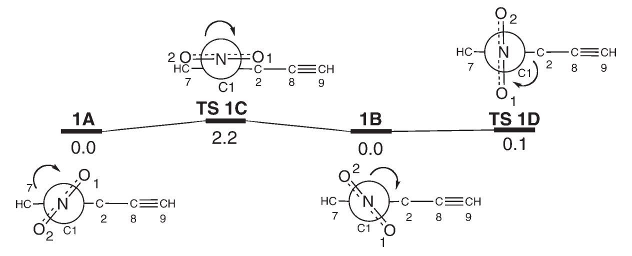


FIGURE 2. PES corresponding to the conformational analysis of **1A** and **1B** calculated at uB3LYP/6-31G**. Enthalpy values including ZPE are expressed in kcal/mol.

Planar Chirality. By a careful search of conformational space, we found that **1A** and **1B** are related to each other by rotation around the torsional angle ω = C2−C1−N−O1 (Figure 2). The absolute value of the torsional angle ω in **1A** and **1B** is 69.0°. Therefore, compounds **1A** and **1B** are atropisomeric due to planar chirality.[19] They are equienergetic but separated by barriers **TS 1C** and **TS 1D**. The energies of **1A,B** and **TS 1C,D** lie within 2.2 kcal/mol of each other. We located a transition structure **TS (1C−1P$_{\mathrm{S}}$)** for the Bergman cyclization of **1A** and **1B**. The intrinsic reaction coordinate (IRC) calculations revealed that **TS (1C−1P$_{\mathrm{S}}$)** connects **TS 1C** and **1P$_{\mathrm{S}}$** (Figure 3).[12] Both saddle points **TS 1C** and **TS (1C−1P$_{\mathrm{S}}$)** are true transition structures as they each bear one imaginary frequency. The visualization of these frequencies reveals that the displacement vectors in **TS 1C** are engaged in the *in* and *out* of plane motion of the NO_2 group (Figure 4A), while in **TS (1C−1P$_{\mathrm{S}}$)** the displacement of C9 and C10 atoms occur simultaneously, in opposite directions, with minute but observable motion of the C9−H and C10−H bonds. Two directly connected saddle points provide the evidence of the PES bifurcation, which is characteristic of the two-step-no-intermediate mechanism.[20] Analogous potential energy surfaces with uphill bifurcation include cyclooctatetraene isomerization[21] and nitrosimine deazetization.[22]

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(16) Nozoe assigned a 7-membered tropolone structure to the natural product hinokitiol: (a) Nozoe, T. *Bull. Chem. Soc. Jpn.* **1936**, *11*, 295–298. (b) Nozoe, T.; Katsura, S. *Bull. Chem. Soc. Jpn.* **1944**, *64*, 181–185. (c) Asao, T.; Itô, S.; Murata, I. *Eur. J. Org. Chem.* **2004**, *2004*, 899–928. (d) Bentley, R. *Nat. Prod. Rep.* **2008**, *25*, 118–138.

(17) (a) Breslow, R. *Acc. Chem. Res.* **1973**, *6*, 393–398. (b) Gogonea, V.; Schleyer, P. v. R.; Schreiner, P. R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1945–1948. (c) Allen, A. D.; Tidwell, T. T. *Chem. Rev.* **2001**, *101*, 1333–1348.

(18) Okamoto, K.; Takeuchi, K.; Komatsu, K.; Kubota, Y.; Ohara, R.; Arima, M.; Takahashi, K.; Waki, Y.; Shirai, S. *Tetrahedron* **1983**, *39*, 4011–4024.

(19) Lioyed-Williams, P.; Giralt, E. *Chem. Soc. Rev.* **2001**, *30*, 145–157.

(20) (a) Singleton, D. A.; Hang, C.; Szymanski, M. J.; Greenwald, E. E. *J. Am. Chem. Soc.* **2003**, *125*, 1176–1177. (b) Ess, D. H.; Wheeler, S. E.; Iafe, R. G.; Xu, L.; Çelebi-Ölçüm, N.; Houk, K. N. *Angew. Chem., Int. Ed.* **2008**, *47*, 7592–7601. (c) Hong, Y. J.; Tantillo, D. J. *Nature Chem.* **2009**, *1*, 384–389. and references cited therein.

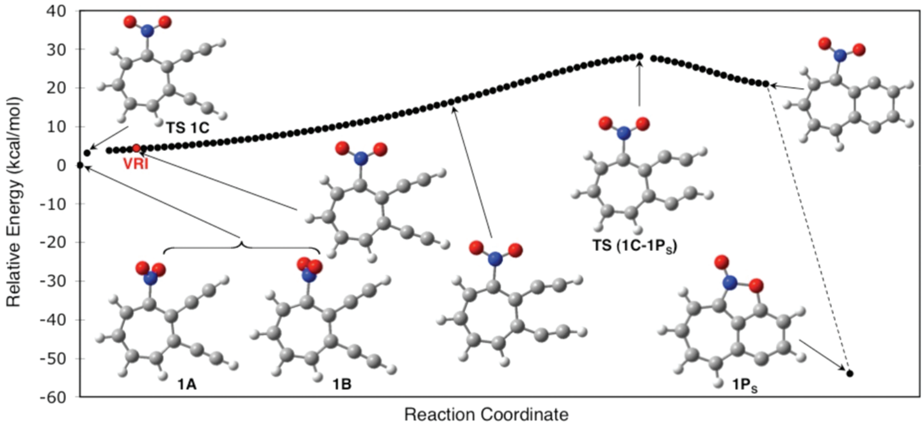
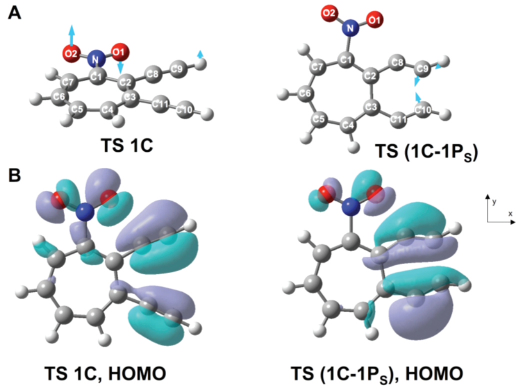


FIGURE 3. Reaction pathway through **TS (1C-1P$_S$)** generated using IRC calculations at the uB3LYP/6-31G** level of theory. The direct connection of **TS (1C-1PS)** and **TS 1C** is labeled. Energies do not include ZPE.



TS 1C

TS (1C-1P$_S$)

TS 1C, HOMO

TS (1C-1P$_S$), HOMO

FIGURE 4. uB3LYP/6-31G**-optimized geometries of **TS 1C** and **TS (1C-1P$_S$)** with (A) displacement vectors shown in blue and (B) HOMOs (isovalue = 0.025).

The minimum energy path (MEP) and the valley-ridge inflection (VRI)[20] for this unstable ridge were estimated from an IRC calculation. We determined the number of the negative frequencies for each point of the IRC pathway connecting **TS (1A−1Ps)** and **TS 1C** and found that the last five points nearest to **TS 1C** each contained one. The analysis of the frequency modes for each of these structures revealed that in principle any of them could connect **1A** and **1B**. The structure closest to **TS (1A−1Ps)** indicates the probable VRI site (Figure 3).

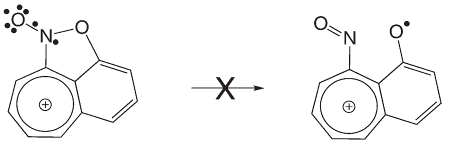
The C−O Bonding Process and Spin States of Product. The in-plane orientation of the NO$_2$ group in the saddle point **TS 1C** causes the repulsion between the lone pair on the oxygen atom and the in-plane π-orbital of the vicinal acetylene C(8)≡C(9)H (Figure 4B). The TS ridge shortens the C9−C10 bond distance *d* of **TS (1C−1P$_S$)** compared to minima **1A** and **1B**. **TS (1C−1P$_S$)** (Figure 4B) shows antibonding MO interactions corresponding to the pericyclic rearrangement of the enediyne moiety and contribution from the oxygen lone-pair orbital. The C8−O1 and C9−C10 distances in **TS (1C−1P$_S$)** are shorter than in **TS 1C**, by 0.20 and 1.70 Å, respectively, because nonbonding orbital at oxygen O1 begins to interact with C8 where the unpaired electron is developing while cleaved in-plane alkyne π orbitals begin to form C9−C10 σ bond.[23]

Because of the O1−C8 bond formation, one of the nonbonding electrons of the in-plane lone pair at O1 has to transfer into the orthogonal π-orbital. This situation is quite comparable to electronic effects in the radical anionic Bergman cyclization of (*Z*)-3-ene-1,5-diyne where the opposite is observed and the electron is transferred from the out-of-plane π-system to the in-plane nonbonding MOs.[24]

Singlet nitroxide diradical **1P$_S$** has $< S^2 > = 1.03$, and its formation is exothermic by 48.9 kcal/mol, which makes this Bergman cyclization irreversible. The high stability of **1P$_S$** is due to the three-electron interaction with the lone-pair electrons at O2, thereby facilitating the Bergman cyclization.

Our data show that $\Delta E_{\mathrm{S-T,adiabatic}} = 1.3$ kcal/mol.[25] The positive value of the singlet−triplet (S−T) gap indicates modest stability of the triplet state **1P$_T$** over the singlet species **1P$_S$** since through-bond coupling and interactions between the unpaired electrons in both **1P$_S$** and **1P$_T$** are absent.[9]

Our calculations also do not a show a minimum optimized structure of a nitroso/phenoxy radical pair arising from **1P$_T$−H**. All attempts to homolyze the N−O bond led to the regeneration of **1P$_T$−H**.



1P$_T$-H **nitroso/phenoxy radical**

Parent and Related Systems. Taking into account the 2.2 kcal/mol of the barrier for the rotation of the NO$_2$ group, the barrier for the formation of **1P$_S$** is 26.5 kcal/mol and is thus 2.0 kcal/mol lower than the barrier for the cyclization of the parent 1,2-diethynylnitrotropylium **2** (Figure 5). Cyclization of **2** is endothermic by 10.1 kcal/mol.

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[21] Wenthold, P. G.; Hrovat, D. A.; Borden, W. T.; Lineberger, W. C. *Science* **1996**, *272*, 1456–1459.

[22] Bartsch, R. A.; Chae, Y. M.; Ham, S.; Birney, D. M. *J. Am. Chem. Soc.* **2001**, *123*, 7479–7486.

[23] (a) Galbraith, J. M.; Schreiner, P. R.; Harris, N.; Wei, W.; Wittkopp, A.; Shaik, S. *Chem.—Eur. J.* **2000**, *6*, 1446–1454. (b) Alabugin, I. V.; Manoharan, M. *J. Phys. Chem. A* **2003**, *107*, 3363–3371.

[24] Alabugin, I. V.; Manoharan, M. *J. Am. Chem. Soc.* **2003**, *125*, 4495–4509.

[25] The results with the 6-31+G(d,p) and 6-311+G(d,p) basis sets confirm the triplet to be more stable than the singlet by 1.3 and 1.4 kcal/mol, respectively.

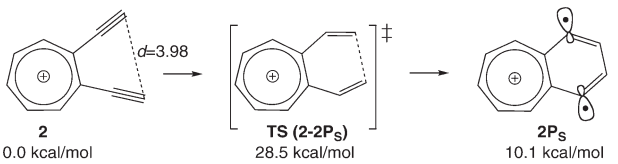


FIGURE 5. Bergman cyclization of 1,2-diethynylnitrotropylium **2** calculated at uB3LYP/6-31G**. Reported enthalpy values include ZPE corrections.

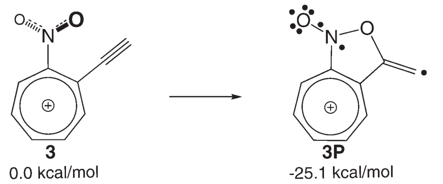


FIGURE 6. C−O bond formation in **3**, a simplified *o*-nitro monoalkyne analogue of **1A/1B** at uB3LYP/6-31G**. Reported enthalpy values include ZPE corrections.

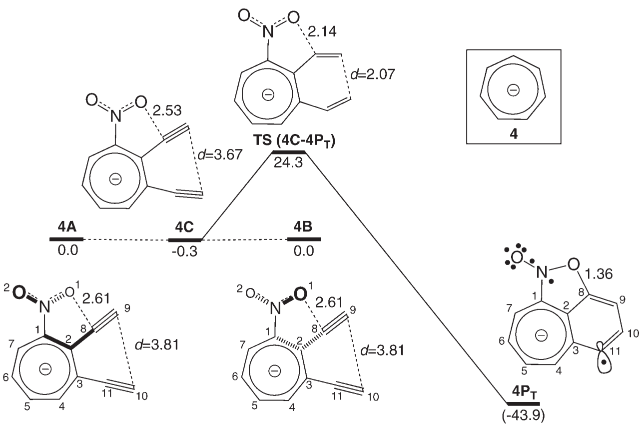
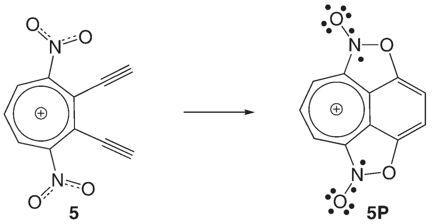


FIGURE 7. PES for the cyclization of the triplet state **4C** calculated at uB3LYP/6-31G**. Enthalpy values include ZPE and are given in kcal/mol, while bond distances are given in Å.

Our computations reveal that the C−O bond formation in the simplified *o*-nitro monoalkyne analogue **3** is exothermic by only $\Delta H = -25.1$ kcal/mol (Figure 6). Hence, when the C8−O1 bond formation is coupled with the Bergman cyclization in 2,3-diethynyl-1-nitrotropylium ion **1A,B**, the system releases an additional 23.8 kcal/mol ($\Delta H = -48.9$ kcal/mol).

We investigated the effect of charge by replacing the tropylium ion framework in structures **1A/1B**, **TS 1C**, **TS (1C−1P$_S$)**, and **1P$_S$** in Figure 1 with the planar D_{7h} triplet-state cycloheptatrienyl anion **4**[17] and by reoptimizing. Comparison of Figures 1 and 7 shows that going from a positive charge to a negative charge does not play a significant role in the cyclization process. Triplet state **4C** cyclizes with a barrier of 24.6 kcal/mol. Nearby minima (**4A** and **4B**) possess puckered rings (either θ = C4−C3−C2−C1 = 10.1° or −10.1°, respectively) and −C8≡C9−H distorted away from the plane of the molecule by η = C11−C3−C2−C8 = 13.2° and −13.2°, respectively. The process leading to triplet **4P$_T$** is exothermic by 43.6 kcal/mol, which is similar in magnitude to the tropylium ion system in Figure 1. The transition structure **TS (4C−4P$_T$)** corresponding to the Bergman cyclization, which connects planar **4C** and **4P$_T$** was confirmed by IRC.

A mechanistically interesting extension of **1A,B** is diyne **5** that would lead to the dinitroxide diradical ion **5P**, which could be of interest in an EPR experiment but would eliminate the radical at C11 site in **1P$_T$**, thus the reactive carbon radical that leads to DNA cleavage.



5 **5P**

In conclusion, the spin density delocalization from the nitroxide **1P$_T$** derived from the Bergman cyclization provides paramagnetic coupling (an important feature of species detectable by EPR spectroscopy). This greatly improved stability of the diradical, which makes the corresponding monohydrogenated **1P$_T$−H** a potentially useful probe of structure and dynamics of enediyne molecules to monitor drug interactions.

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Supporting Information Available: Additional details on calculations at uB3LYP/6-31G** and results obtained with BLYP/6-31G**. This material is available free of charge via the Internet at http://pubs.acs.org.