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A New Thermally Generated Biradical Capable of Intermolecular Hydrogen Atom Abstraction

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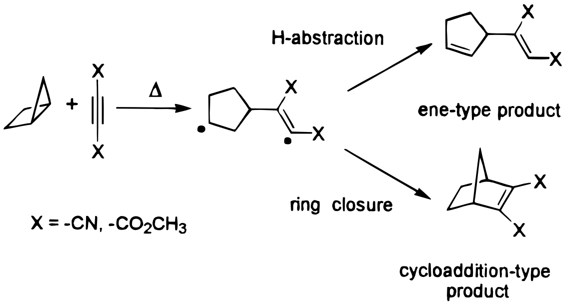
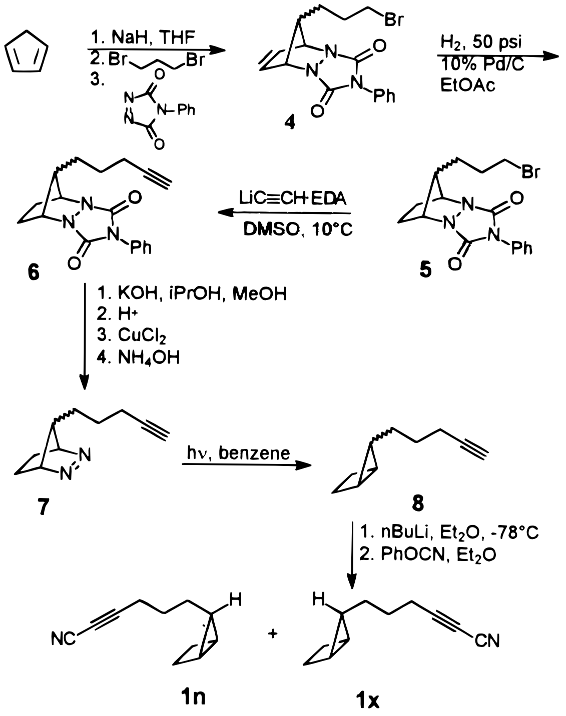
Nonstabilized yet interceptible biradicals have attracted a great deal of recent interest, because species of this kind are believed to constitute the active forms of such DNA-cleaving antitumor agents as calicheamicin, esperamicin, dynemicin, and neocarzinostatin.[1] Models for the active states of these complex molecules are the much simpler species 1,4-didehydrobenzene[2] and α,3-didehydrotoluene,[3] which are formed by the thermal cycloaromatization of 1,5-hexadiyn-3-ene and hepta-1,2,4-trien-6-yne, respectively. These biradicals are largely unstabilized and are sterically prevented from undergoing intramolecular bond formation, a combination of features making them extremely reactive toward bimolecular hydrogen abstraction and thereby constituting a crucial component of their potency as DNA-cleaving agents. Here we report a new biradical in this class, the didehydromethyleneindane **17**, which is formed from the thermal intramolecular reaction of the substituted bicyclo[2.1.0]pentane **1x**.

The intermolecular additions of electron-deficient olefins and acetylenes to bicyclo[2.1.0]pentane were studied extensively by Gassman and Mansfield[4] who found that both cycloaddition and ene-type products were formed via a proposed biradical intermediate:

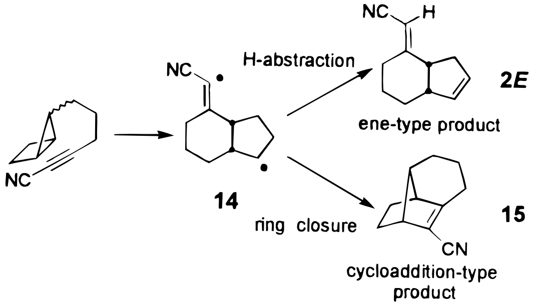


Here, in order to investigate its intramolecular addition reaction, we tethered a cyanoacetylene group to the bicyclopentane methano bridge. It was hoped that the alkyne would add to the strained bond from the exo face in the case of **1x** and the endo face in the case of **1n**. A mixture[5] of the two epimeric bicyclopentanes was synthesized as shown in Scheme 1. When the mixture was pyrolyzed at 160 °C for 16 h in the gas phase, all of the starting material was consumed. A considerable amount of brown polymeric material was formed along with three nonpolymeric products. The major product, comprising about 70% of the mixture, had spectral data consistent with **2*E***. In analogy to Gassman and Mansfield's results, this compound could be formed via the biradical **14**, which could then either close to give the strained anti-Bredt cycloaddition product **15** or undergo intramolecular hydrogen atom abstraction to give the ene-type product **2*E***.

Scheme 1



There was no evidence of any **15** in the reaction mixture, presumably because it is too strained. That **2*E*** is the correct structure of this primary product was confirmed by independent synthesis. The known *cis*-bicyclo[4.3.0]non-7-en-2-one[6] was converted to a mixture of the two cyanoalkenes **2*E*** and **2*Z*** via a Wadsworth−Horner−Emmons reaction.[7] Although this mixture was inseparable, one of these isomers (assumed to be the *E* isomer) and the major pyrolysis product exhibited identical ^{13}C NMR and ^{1}H NMR spectra, mass spectra, and GC retention times. The other, presumably *Z*, isomer was not seen in the pyrolysis reaction.



Interestingly, however, when the pyrolysis was run for shorter times and followed by GC, the peak corresponding to the exo epimer **1x** was found to disappear more quickly

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(1) Nicolaou, K. C.; Smith, A. L. In *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; VCH: Weinheim, 1995.

(2) Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25.

(3) Myers, A. G.; Dragovich, P. S.; Kuo, E. Y. *J. Am. Chem. Soc.* **1992**, *90*, 9369.

(4) (a) Gassman, P. G.; Mansfield, K. T. *J. Am. Chem. Soc.* **1968**, *90*, 1517. (b) Gassman, P. G.; Mansfield, K. T. *J. Am. Chem. Soc.* **1968**, *90*, 1524. (c) Gassman, P. G.; Mansfield, K. T.; Murphy, T. J. *J. Am. Chem. Soc.* **1969**, *91*, 1684. (d) Gassman, P. G. *Acc. Chem. Res.* **1971**, *4*, 128.

(5) The exact ratios of the epimers depended on the relative amounts of the syn and anti isomers in the azo precursor but were typically between 1 and 1.35 to 1 in favor of the exo epimer.

(6) (a) Wollenberg, R. H. PhD. Dissertation, Harvard University, 1977. (b) Hudlicky, T.; Koszyk, F. J.; Dochwat, D. M.; Cantrell, G. L. *J. Org. Chem.* **1981**, *46*, 2911.

(7) See Supporting Information for details.

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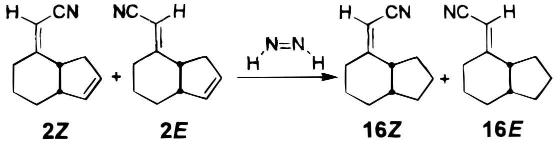
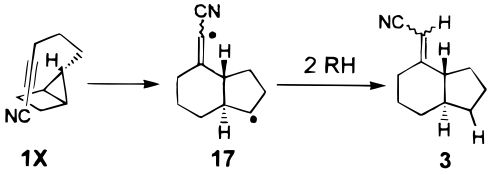
than that corresponding to **1n**. At short reaction times (1−4 h) there was relatively little **2*E*** formed. Instead, the two products that had been present in much smaller quantities after the 16 h pyrolysis now comprised about two-thirds of the nonpolymeric product mixture (with **2*E*** and very small amounts of other products making up the other third). This would appear to imply that the exo epimer was reacting more quickly than the endo epimer to produce these other, unidentified products. One of these formerly minor products was present in an approximately 3:1 ratio over the other. The products were determined by GC-MS analysis to have acquired 2 extra mass units, but were spectroscopically very similar to **2**, except that the endocyclic olefin protons were missing from their ^{1}H NMR spectra. That these products did not simply come from the biradical intermediate **14** being trapped before it underwent intramolecular hydrogen atom abstraction was demonstrated by selectively reducing the endocyclic double bonds of **2*E*** and **2*Z***.



The reduction products **16*E*** and **16*Z*** had ^{13}C NMR and ^{1}H NMR spectra that were very similar to, but not identical with, those of the unknown products.

In every case that the stereochemistry of the intermolecular addition of electron-deficient multiple bonds and benzyne to the strained bonds of bicyclo[2.1.0]pentane or bicyclo[1.1.0]butane has been studied,[4c,d,8] it has been found that attack occurs from its "backside", or endo face. It was hoped that with the electrophile tethered exo to the bicyclic ring system (**1x**) endo attack would be sterically very unfavorable and that attack from the exo face would occur instead. However, if a backside attack were to occur anyway, the result would be **17**, a biradical intermediate with a trans ring junction.



Models suggest that **17** would be too conformationally constrained either to ring close or to undergo intramolecular hydrogen atom abstraction. Such a "frustrated" biradical would, like 1,4-didehydrobenzene and α,3-didehydrotoluene, have no choice but to abstract hydrogen atoms from other molecules in its surrounding environment in order to give the closed shell products **3** (which differ from **16** only by virtue of their trans ring junctions).

That the two isomers of **3** are indeed the second and third products was again confirmed by independent synthesis.[7] Comparison of spectral data and GC retention times of the independently synthesized material and pyrolysis products showed them to be identical. Both isomers of **3** were seen in the pyrolysis mixture, as would be expected from the intermediacy of a long-lived vinyl radical. As an additional piece of evidence for a long-lived biradical intermediate, pyrolyses conducted in benzene, a very poor hydrogen atom donor, quickly turned yellow and produced a large amount of polymeric material. When methanol, a better hydrogen atom donor, was used as a solvent instead, much less color change and polymeric material was observed.[9]

A final point that needs to be addressed concerns the mechanism of this reaction. There are two notable features. The first is that there seems to be an overwhelming preference for backside attack, even in the present case where it would appear to be sterically much less favored. The second is that the reactivity of the multiple bond seems to be directly related to how electron-deficient it is.[4] A possible explanation for these facts is that a thermal electron transfer mechanism is occurring. The strained central bonds of bicyclo[2.1.0]pentane and bicyclo[1.1.0]butane easily undergo photoinduced electron transfer reactions.[10] One could imagine that in the present work an electron could be thermally induced to transfer to the cyanoacetylene from the strained bond, leaving a radical cation and generating a radical anion. Attack of this radical anion on the one-electron bond would give **14** and **17**, the biradicals proposed earlier. There are several cases of nucleophilic attacks on similar radical cations generated by photoinduced electron transfer. These reactions occur exclusively with inversion of configuration.[11] If a nucleophilic attack of the cyanoacetylene radical anion were to occur at the bridgehead position of the radical cation, the endo isomer **1n** would give a biradical with a cis ring junction and the exo isomer **1x** would give a biradical with a trans ring junction, which would be fully consistent with the observed results.

In summary, pyrolysis of the endo-substituted bicyclopentane derivative **1n** gives an intermediate biradical that, by virtue of its cis ring junction, can undergo an intramolecular hydrogen atom abstraction to give a stable, closed shell product. Pyrolysis of the exo-substituted isomer **1x**, on the other hand, gives a "frustrated" biradical intermediate that is unable to undergo intramolecular reaction and must acquire hydrogen atoms from its environment. Thus, **17** is a new addition to the interesting class of nonstablized but long-lived biradicals headed by 1,4-didehydrobenzene.

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Supporting Information Available: Schemes for independent syntheses, experimental details of the syntheses and pyrolyses, and ^{13}C NMR spectra of all new compounds and ^{1}H spectra of **1** and the pyrolysis mixture (28 pages).

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[8] (a) Roth, W. R.; Martin, M. *Tetrahedron Lett.* **1967**, 4695. (b) Gassman, P. G.; Richmond, G. D. *J. Am. Chem. Soc.* **1970**, *92*, 2090. (c) Pomerantz, M.; Wilke, R. N.; Gruber, G. W.; Roy, U. *J. Am. Chem. Soc.* **1972**, *94*, 2752. (d) Chang, M. H.; Jain, R.; Dougherty, D. A. *J. Am. Chem. Soc.* **1984**, *106*, 4211.

[9] There were also small amounts of other, higher molecular weight products (presumably formed by reaction of starting material, intermediates, or products with the solvent). Attempts to isolate and identify these products were unsucessful. GC-MS analysis of the product mixture did, however, show that about three-quarters of **3** had incorporated two deuteriums and that the rest had incorporated a single deuterium. These deuteriums almost certainly came from the solvent, further supporting the existence of an interceptible biradical intermediate.

[10] Gassman, P. G. In *Photoinduced Electron Transfer*; Fox, M. A., Chanon, M., Eds.; Elsevier: Amsterdam, 1988; Part C.

[11] (a) Gassman, P. G.; Olson, K. D.; Walter, L.; Yamaguchi, R. *J. Am. Chem. Soc.* **1981**, *103*, 4977. (b) Dinnocenzo, J. P.; Todd, W. P.; Simpson, T. R.; Gould, I. R. *J. Am. Chem. Soc.* **1990**, *112*, 2462.