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Anionic Cyclization of a Cross-Conjugated Enediyne

Lior Eshdat,† Harald Berger,‡ Henning Hopf,*,‡ and Mordecai Rabinovitz*,†

Department of Organic Chemistry, The Hebrew University of Jerusalem, 91904 Jerusalem, Israel, and Institute of Organic Chemistry, Technical University of Braunschweig, Hagenring 30 D-38106 Braunschweig, Germany

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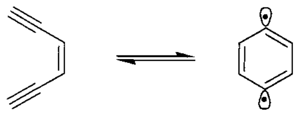
The Bergman cyclization of enediynes[1] (**1**) plays the key role in the *mode of action* of the enediyne antitumor drugs, such as calicheamicin γ_1.[2] The cyclization is not spontaneous at ambient temperatures. It takes place in vivo, after a trigger reaction brings the edges of the enediyne with its six-conjugated π e$^-$ close enough, so that cyclization forms the active benzene biradical.[3]

Cross-conjugated enediynes (**2**), also referred to as Y-enediynes,[4] are branched isomers of linear enediynes. Compounds of this class serve as building blocks of novel carbon allotropes,[5] conjugated polymers,[5,6] and radialenes,[7] and are also used as precursors for bowl-shaped fullerene fragments.[8] Unlike linear enediynes, cross-conjugated enediynes cannot follow the Bergman cycloaromatization pathway because five carbon atoms are involved (i.e., the methylenediyne moiety) with only five π e$^-$, which is insufficient for aromatization. However, under reductive conditions the cyclization may be feasible by generating a product with a Hückel number of π electrons. In this study we illustrate this principle and demonstrate for the first time an anionic cyclization of a cross-conjugated enediyne that results in formation of a five-membered ring.[9−11]



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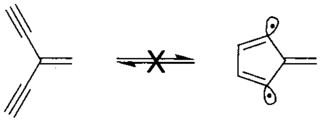

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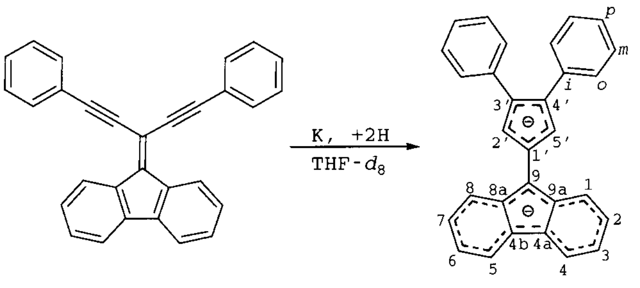
Reduction of **3**[12] with potassium was carried out in vacuo at 258 K in an extended NMR tube.[13] Brief contact between the organic solution and the potassium mirror broadens the NMR spectrum, which is attributed to formation of a radical anion. Further reduction yields a highly complex NMR spectrum, and after a few hours, during which the solution changes its color several times, it finally turns brown together with brown precipitation, and a clear NMR spectrum of a single species is observed.

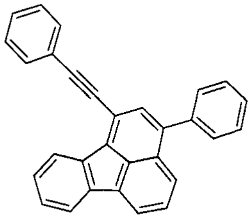
Full assignment of the ^{1}H and ^{13}C NMR spectra of the final species using 2D techniques as well as characterization of the oxidized product leads to the conclusion that the result of reduction of **3** is a cycloaromatization product, i.e., 3′,4′-diphenyldibenzo-[*a,c*]pentafulvalene dianion (**4**$^{2-}$).[14]



3 **4**$^{2-}$

The ^{1}H NMR spectrum of **4**$^{2-}$ shows ABCD and AA′BB′C patterns that correspond to the fluorene and the phenyl groups, respectively, and a singlet at δ 6.52, which is not in line with the structure of the starting material. This singlet shows a through-space correlation to H-1/H-8 and H-*ortho*, and a C−H correlation to a sp^2 hybridized carbon atom resonating at δ 118.9, to which it also shows a long-range (three-bond) C−H correlation. Two other long-range C−H correlations are to C-*ipso* and C-3′/C-4′. The latter correlation is possible only if the singlet is attributed to a hydrogen atom attached to a five-membered ring that is located between the fluorene and the phenyl rings, i.e., H-2′/H-5′.

Under thermal conditions **3** undergoes a so-called Hopf cyclization[15] to yield **5**.[12] Recurrence of such a cyclization under the above reductive conditions, either on one side or both (to yield **5**$^{2-}$ or **6**$^{2-}$, respectively), is ruled out on the grounds of the evidence of formation of a five-membered ring, the existence of a single fluorenyl ABCD pattern, and the through-space correlation between H-2′/H-5′ and H-1/H-8.



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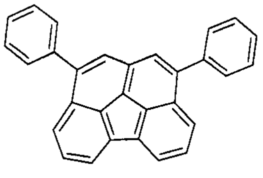

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The transformation of the triple bonds into part of a five-membered ring is indicated by the absence of ^{13}C NMR chemical shifts that are typical for sp hybridized carbons. The absence of the anisotropic effect of the acetylene groups accounts for the similarity in the chemical shifts of H-1 and H-4 (δ 8.04 and 8.02, respectively), whereas in the starting material **3**, H-1 is shifted

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* Corresponding authors. E-mail: Mordecai@vms.huji.ac.il and H.Hopf@tu-bs.de.
† The Hebrew University of Jerusalem.
‡ Technical University of Braunschweig.

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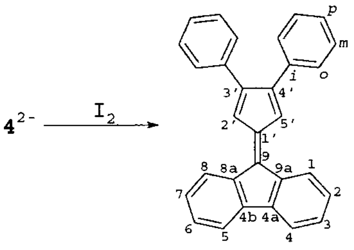
Table 1. ^{1}H and ^{13}C NMR Chemical Shifts (ppm) of **4** and the Potassium Salt of **4**$^{2-}$ [a]

		position:													
		1,8	2,7	3,6	4,5	4a,4b	9	8a,9a	1′	2′,5′	3′,4′	ipso	ortho	meta	para
4	δ_C	128.0	128.4	130.6	128.8	143.0	143.0	139.6	142.2	122.5	137.2	149.6	128.7	129.3	128.4
	δ_H	8.30	7.34	7.40	7.77					7.41			7.30	7.37	7.30
4^{2-}	δ_C	114.5	119.7	108.1	118.8	123.2	95.6	133.3	119.0	107.5	118.9	144.2	127.2	127.3	120.2
	δ_H	7.98	6.87	6.42	7.93					6.52			7.45	7.01	6.75
	$\Delta\delta_C$	13.5	8.7	22.5	2.0	19.8	47.4	6.3	23.2	15.0	18.3	5.4	1.5	2.0	8.2

[a] 400.1 and 100.6 MHz (^{1}H and ^{13}C NMR, respectively), THF-d_8, room temperature and 260 K, for **4** and **4**$^{2-}$, respectively.

downfield by 1.1 ppm from H-4 (δ 8.72 and 7.73, respectively) due to this effect.

Quenching the anionic solution with iodine yields neutral reddish-brown oil (32%).[16] It exhibits totally different ^{1}H and ^{13}C NMR spectra than of the starting material **3**, showing no chemical shifts typical of an sp-hybridized carbon. The interpretation of the NMR spectra speaks for **4** as the structure of the neutral hydrocarbon. The HRMS analysis of **4** is in line with the addition of two hydrogen atoms (DCI-HRMS: calcd 381.1643, found 381.1602).



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The reductive cyclization follows a multistep mechanism as evidenced by the multiple color changes, and from observing highly complex NMR spectra of several distinct patterns in equilibrium. The presence of a cyclopentadienyl anion moiety in the product is made possible only if the five carbon atoms of the methylenediyne fragment undergo reduction, cyclization, and proton or hydrogen atom abstraction.[17] We are now attempting to establish the order of these steps and the intermediates involved by both experiment and calculation.

Table 1 shows the differences between the ^{13}C NMR spectra of **4** and **4**$^{2-}$ that are indicative of the charge density residing on each carbon atom.[18] The most striking shift upfield, by 47.4 ppm, is of the acidic C-9. The carbons of the five-membered ring also show a relatively high upfield shift in the anionic state. These two observations are in accord with viewing **4**$^{2-}$ as composed of covalently linked fluorenyl and substituted cyclopentadienyl anions. The phenyl substituents withdraw relatively small amounts of charge from the cyclopentadienyl. The fluorenyl unit exhibits a charge alternation effect,[19] whereas over the cyclopentadienyl ring the charge is almost evenly distributed. The total shift upfield ($\sum\Delta\delta$) sums up to 324 ppm, which is in the expected range for a dianion ($\sum\Delta\delta$ = ca.. 320).[18]

This reaction offers a new approach for the synthesis of fulvalenes. This and other practical points of view are of great interest as are the theoretical and mechanistic aspects of this novel anionic cyclization.

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References

(1) (a) Jones, R. R.; Bergman R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660−1. (b) Bergman R. G. *Acc. Chem. Res.* **1973**, *6*, 25−31. (c) Lockhardt, T. P.; Commita, P. B.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4082−90.
(2) (a) Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1377−1385 and references therein. (b) Hitchcock, S. A.; Chu-Moyer, M. Y.; Boyer, S. H.; Olson, S. H.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 5750−6.
(3) (a) Snyder, J. P. *J. Am. Chem. Soc.* **1989**, *111*, 7630−2. (b) Magnus, P.; Carter, P.; Elliott, J.; Lewis, R.; Harling, J.; Pitterna, T.; Bauta, W. E.; Fortt, S. *J. Am. Chem. Soc.* **1992**, *114*, 2544−59. (c) Jones, L. H.; Harwig, C. W.; Wentworth, P., Jr.; Simeonov, A.; Wentworth, A. D.; Py, S.; Ashley, J. A.; Lerner, R. A.; Janda, K. D. *J. Am. Chem. Soc.* **2001**, *123*, 3607−8.
(4) Kaafarani, B. R.; Neckers, D. C. *Tetrahedron Lett.* **2001**, *42*, 4099−4102.
(5) (a) Diederich, F.; Rubin, Y. *Angew. Chem., Int. Ed. Engl.* **1992**, *32*, 1101−23 and references therein. (b) Diederich, F. *Pure Appl. Chem.* **1999**, *71*, 265−273. (c) Zhao, Y.; Tykwinski, R. R *J. Am. Chem. Soc.* **1999**, *121*, 458−9.
(6) Schenning, A. P. H. J.; Arndt, J.-D.; Ito, M.; Stoddart, A.; Schreiber, M.; Siemsen, P.; Martin, R. E.; Boudon, C.; Gisselbrecht, J.-P.; Gross, M.; Gramlich, V.; Diederich, F. *Helv. Chim. Acta* **2001**, *84*, 296−334 and refernces cited therein.
(7) (a) Nielsen, M. B.; Schreiber, M.; Baek, Y. G.; Seiler, P.; Lecomte, S.; Boudon, C.; Tykwinski, R. R.; Gisselbrecht, J.-P.; Gramlich, V.; Skinner, P. J.; Bosshard, C.; Günter, P.; Gross, M.; Diederich, F. *Chem. Eur. J.* **2001**, *7*, 3263−80. (b) Eisler, S.; Tykwinski, R. R. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1940−3. (c) Lange, T.; Gramlich, V.; Amrein, W.; Diederich, F.; Gross, M.; Boudon, C.; Gisselbrecht, J.-P. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 805−9.
(8) Zimmermann, G.; Nüchter, U.; Hagen, S.; Nüchter, M. *Tetrahedron Lett.* **1994**, *35*, 4747−50.
(9) Tetra(*tert*-butylethynyl)ethylene cyclizes twice into *six*-membered rings to form a naphthalene derivative under reductive conditions: Hauptmann, H.; Mader, M. *Tetrahedron Lett.* **1980**, *21*, 897−8.
(10) Anionic cyclization of $\sigma^*-\pi^*$ conjugated diynes yielding five-membered rings: (a) Tamao, K.; Yamaguchi, S.; Shiro, M. *J. Am. Chem. Soc.* **1994**, *116*, 11715−22. Anionic cyclization of nonconjugated diynes yielding five-membered rings: (b) Tamao, K.; Yamaguchi, S. *Pure Appl. Chem.* **1996**, *68*, 139−144. (c) Yamaguchi, S.; Tamao, K. *Tetrahedron Lett.* **1996**, *37*, 2983−6.
(11) (a) Anionic cyclization in the exo−endo mode (see ref 10a) of linear-conjugated enediyne yields fulvene: Whitlock, H. W., Jr.; Sandvick, P. E.; Overman, L. E.; Reichardt, P. B. *J. Org. Chem.* **1969**, *34*, 879−886. (b) Anionic cyclization in the exo−endo mode of a cyclotriyne yields a fulvalene dianion derivative: Youngs, W. J.; Djebli, A.; Tessier, C. A. *Organomatallics* **1991**, *10*, 2089−90.
(12) Hopf, H.; Berger, H.; Zimmermann, G.; Nüchter, U.; Jones, P. G.; Dix, I. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1187−90.
(13) Each sample contained 6 mg of **3** in 0.7 mL of THF-d_8. The method for carrying out controlled reduction by alkali metals was previously described: Eshdat, L.; Ayalon, A.; Beust, R.; Shenhar, R.; Rabinovitz, M. *J. Am. Chem. Soc.* **2000**, *122*, 12637−45.
(14) Diederich et al. reported (see ref 7c) that the dianion of hexa-(trimethylsilylethynyl)[3]radialene undergoes a chemical modification. We suggest that this modification is an anionic cycloaromatization of the cross-conjugated enediyne moieties.
(15) For a recent review please see: Zimmermann, G. *Eur. J. Org. Chem.* **2001**, 457−471.
(16) The quench product is unstable due to oxidation of the C1′−C9 double bond.
(17) No deuterium signals in ^{2}D NMR experiments were observed, except for those of THF-d_8 that remained intact. We therefore assume that hydrogen atoms or protons were not abstracted from the solvent but rather from one of the reaction intermediates or from the reduction products of traces of water.
(18) (a) Müllen, K. *Chem. Rev.* **1984**, *84*, 603−646. (b) Rabinovitz, M. *Top. Curr, Chem.* **1988**, *146*, 99−169.
(19) (a) Klein, J. *Tetrahedron* **1983**, *39*, 2733−59. (b) Cohen, Y.; Klein, J.; Rabinovitz, M. *J. Am. Chem. Soc.* **1988**, *110*, 4634−40.

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