

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/231465426>

# Inhibition and Acceleration of the Bergman Cycloaromatization Reaction by the Pentamethylcyclopentadienyl Ruthenium Cation

ARTICLE *in* JOURNAL OF THE AMERICAN CHEMICAL SOCIETY · NOVEMBER 2000

Impact Factor: 12.11 · DOI: 10.1021/ja005514c

---

CITATIONS

37

---

READS

8

3 AUTHORS, INCLUDING:



[Joseph M O'Connor](#)

University of California, San Diego

101 PUBLICATIONS 2,071 CITATIONS

SEE PROFILE



[Peter Gantzel](#)

University of California, San Diego

94 PUBLICATIONS 2,995 CITATIONS

SEE PROFILE

# Inhibition and Acceleration of the Bergman Cycloaromatization Reaction by the Pentamethylcyclopentadienyl Ruthenium Cation

Joseph M. O'Connor,\* Linda I. Lee, and Peter Gantzel

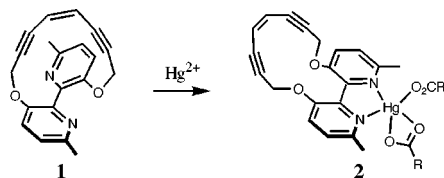
Department of Chemistry and Biochemistry  
0358 University of California, San Diego  
9500 Gilman Drive, La Jolla, California 92093-0358

Arnold L. Rheingold\* and Kin-Chung Lam

Department of Chemistry, University of Delaware  
Newark, Delaware 19716

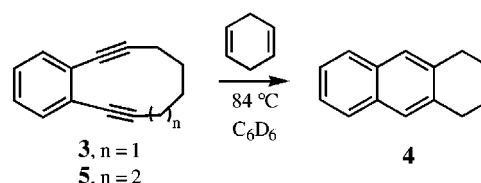
Received August 7, 2000

The fascinating mode of action exhibited by enediyne antitumor antibiotics has stimulated research into methods for controlling cycloaromatization of enediynes to 1,4-aryldiradicals (Bergman cycloaromatization<sup>1</sup>).<sup>2</sup> Among the ingenious methods developed for activation of cyclic enediynes is metal ion coordination.<sup>3,4</sup> In this approach, the activation energy for cyclization is lowered by metal ion coordination to heteroatoms judiciously situated within the enediyne framework. For example, complexation of Hg(OCOCF<sub>3</sub>)<sub>2</sub> to the 2,2'-bipyridine unit within cyclic enediyne **1** leads to a conformational change in the enediyne core **2** and lowers the cyclization temperature by ~100 °C.<sup>3b</sup> Here we report (1) the first conclusive evidence that metal coordination to the ene function of enediynes retards the rate of Bergman cycloaromatization,<sup>5,6</sup> and (2) a new organometallic trigger for the cycloaromatization of cyclic enediynes, one which does not require heteroatoms for metal ligation.<sup>7</sup>



Semmelhack previously reported that heating benzene-*d*<sub>6</sub> solutions of 3,4-benzo-cyclodec-3-ene-1,5-diyne (**3**) and 1,4-cyclohexadiene (0.5 M) at 84 °C gave tetrahydroanthracene (**4**) with a half-life of 24 h.<sup>8</sup> The 11-membered ring analogue **5** failed to undergo a thermal Bergman cyclization.

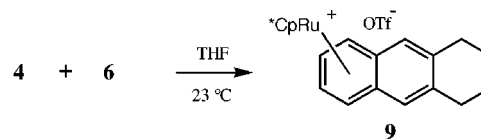
- (1) Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660.  
(2) (a) Maier, M. E.; Bosse, F.; Niestroj, A. J. *Eur. J. Org. Chem.* **1999**, *1*, 3277. (b) Semmelhack, M. F.; Neu, T.; Foubelo, F. *J. Org. Chem.* **1994**, *59*, 5038.  
(3) (a) McNair, A. M.; Schrenk, J. L.; Mann, K. R. *Inorg. Chem.* **1984**, *23*, 2633. (b) Fagan, P. J.; Ward, M. D.; Calabrese, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 1698. (c) Seiders, T. J.; Baldrige, K. K.; O'Connor, J. M.; Siegel, J. S. *J. Am. Chem. Soc.* **1997**, *119*, 4781.  
(4) For "C<sub>5</sub>Me<sub>5</sub>Ru<sup>+</sup>"-mediated aromatization of alkenes, see: Chaudret, B. *Bull. Soc. Chim. Fr.* **1995**, *132*, 268.  
(5) For [(C<sub>5</sub>H<sub>5</sub>)Ru(NCMe)<sub>3</sub>][PF<sub>6</sub>]-catalyzed cyclizations of yne-enones see: Trost, B. M.; Brown, R. E.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 5877.  
(6) Funk, R. L.; Young, E. R. R.; Williams, R. M.; Flanagan, M. F.; Cecil, T. L. *J. Am. Chem. Soc.* **1996**, *118*, 3291.  
(7) In CH<sub>2</sub>Cl<sub>2</sub>, photolysis of [(C<sub>5</sub>Me<sub>5</sub>)Ru(C<sub>6</sub>R<sub>6</sub>)] [PF<sub>6</sub>] (R = H or R = Me) complexes gave no detectable reaction: Schrenk, J. L.; McNair, A. M.; McCormick, R. B.; Mann, K. R. *Inorg. Chem.* **1986**, *25*, 3501.  
(8) Nicolaou, K. C.; Dai, W.-M.; Hong, Y. P.; Tsay, S.-C.; Baldrige, K. K.; Siegel, J. S. *J. Am. Chem. Soc.* **1993**, *115*, 7944.  
(9) (a) Crystal data for **7**: C<sub>25</sub>H<sub>27</sub>F<sub>3</sub>O<sub>3</sub>RuS, orthorhombic, *Fdd2*, *a* = 25.1032(6) Å, *b* = 51.8895(12) Å, *c* = 7.3805(2) Å, *V* = 9613.8(6) Å<sup>3</sup>, *Z* = 16, *T* = 173 K, 4968 reflections and 298 parameters, *R*(*F*) = 0.0465, *wR*(*F*<sup>2</sup>) = 0.1319. (b) Crystal data for **3**: C<sub>14</sub>H<sub>22</sub>, tetragonal, *P4<sub>1</sub>2<sub>1</sub>2*, *a* = 7.916(2) Å, *b* = 7.916(2) Å, *c* = 16.556(6) Å, *V* = 1037.3(6) Å<sup>3</sup>, *Z* = 4, *T* = -87 °C, 818 reflections and 64 parameters, *R*(*F*) = 0.0469, *wR*(*F*<sup>2</sup>) = 0.1120. A less precise X-ray structural analysis of **3** has been reported: Bennett, M. J.; Smith, R. A. *Acta Crystallogr.* **1977**, *B33*, 1123. (c) Crystal data for **9**: C<sub>25</sub>H<sub>26</sub>F<sub>3</sub>O<sub>3</sub>-RuS, orthorhombic, *Pnma*, *a* = 29.2978(8) Å, *b* = 11.4140(3) Å, *c* = 7.4888(2) Å, *V* = 2504.30(18) Å<sup>3</sup>, *Z* = 4, *T* = 223 K, 1759 reflections and 173 parameters, *R*(*F*) = 0.0915, *wR*(*F*<sup>2</sup>) = 0.2920. The triflate counterion is both rotationally and end-for-end disordered. Both ions reside on a crystallographic mirror plane.  
(10) A large excess of Cr(II) has been observed to accelerate the cycloaromatization of a cyclic enediyne: Semmelhack, M. F.; Gu, Y.; Ho, D. M. *Tetrahedron Lett.* **1997**, *38*, 5583.



In an effort to prepare a robust  $\eta^6$ -arene complex of **3** we employed the "super-areneophile" [( $\eta^5$ -C<sub>5</sub>Me<sub>5</sub>)Ru(NCMe)<sub>3</sub>][OTf] (**6**).<sup>9–11</sup> When a THF solution of **3** (50 mg, 54 mM) and **6** (140 mg, 54 mM) was stirred under a nitrogen atmosphere at 23 °C (12 h), the arene complex [( $\eta^5$ -C<sub>5</sub>Me<sub>5</sub>)Ru( $\eta^6$ -3,4-benzocyclodec-3-ene-1,5-diyne)][OTf] (**7**) precipitated from solution as white flakes in 47% unoptimized yield (Scheme 1).

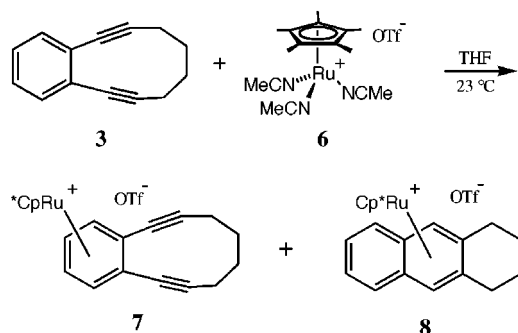
When the reaction of **3** and **6** was monitored by <sup>1</sup>H NMR spectroscopy (CD<sub>2</sub>Cl<sub>2</sub> or THF-*d*<sub>8</sub>), a set of minor resonances was observed in addition to those that arise from **7**. In particular, a singlet at  $\delta$  6.79 (THF-*d*<sub>8</sub>) was attributed to the aromatic hydrogens (residual protio resonances) on the ruthenium-bound central ring of cyclization product **8**.

When THF-*d*<sub>8</sub> or NO<sub>2</sub>CD<sub>3</sub>/CH<sub>3</sub>CN solutions of **7** were heated at 60 °C (72 h), no conversion to **8** was observed by <sup>1</sup>H NMR spectroscopy. Furthermore, the reaction of tetrahydroanthracene (**4**) and **6** in THF (rt, 12 h) gave an 83% isolated yield of arene complex **9**,<sup>15c</sup> which proved to be stable in THF-*d*<sub>8</sub> at 60 °C (72 h). Thus, complex **8** does not arise from either **7** or **9** via ruthenium migration, nor does it arise from in situ formation of **4** and subsequent ruthenium complexation.

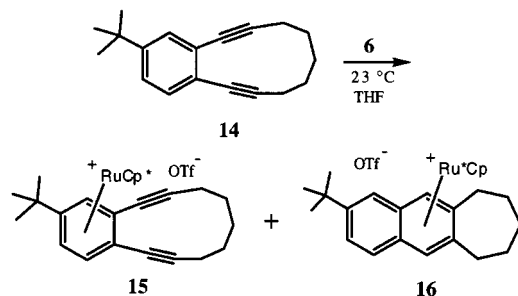


To improve the yield of cycloaromatization product and substantiate the occurrence of a metal-accelerated Bergman cycloaromatization, the substituted enediynes **10** and **11** were examined in reactions with **6**. In the absence of **6**, neither **10** nor **11** undergo a cycloaromatization in THF at room temperature.

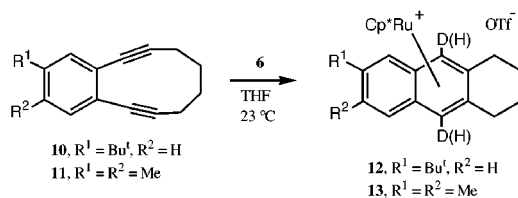
## Scheme 1



## Scheme 2

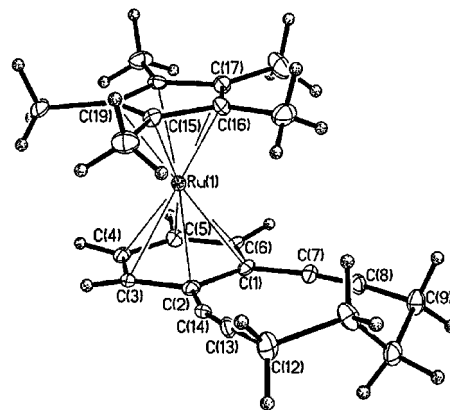


However, when a THF solution of **10** (17 mg, 8.4 mM) and **6** (32 mg, 8.4 mM) was maintained at room temperature for 5 h, the cyclized product **12** was formed and isolated as a yellow solid in 71% yield. In a similar fashion, reaction of enediyne **11** with **6** in THF at room temperature led to isolation of ruthenium arene **13** as yellow solid in 63% yield. Consistent with the formation of a 1,4-diradical intermediate, the reaction of **10** with **6** in THF-*d*<sub>8</sub> gave the cyclized product **12-d** with 79% deuterium incorporation at the aromatic hydrogen positions in the complexed ring.



In an effort to extend this new cycloaromatization reaction to a less strained cyclic enediyne, we examined the reaction of the 11-membered ring enediyne **14** with **6** (Scheme 2). In THF solution **6** (84 mg, 33 mM) and **14** (45 mg, 32 mM) underwent a slow reaction at room temperature over the course of 65 h to give ~42% yield of two C<sub>5</sub>Me<sub>5</sub> containing products in a 2.7:1 ratio. Although the mixture was not separated, on the basis of <sup>1</sup>H NMR spectroscopic data (CDCl<sub>3</sub>), we assign structure **15** [δ 5.71 (s, 1H), 5.96 (d, 1H), 6.31 (dd, 1H)] to the minor product, and cyclized structure **16** [δ 6.41 (s, 1H), 6.44 (s, 1H), 7.33 (d, 1H), 7.52 (d, 1H), 7.71 (dd, 1H)] to the major product. The acyclic enediyne, 4-*tert*-butyl-1,2-di(1-propynyl)benzene, also underwent reaction with **6** over the course of 48 h in THF but gave only the uncyclized arene complex in 71% yield.

The mechanism of this new metal-accelerated Bergman cycloaromatization remains to be established; however, the above results indicate that 1,4-diradicals are involved and point to ruthenium–alkyne interactions as a key feature of the triggering



**Figure 1.** ORTEP diagram (30% thermal ellipsoid probabilities) for (**7**). Selected bond lengths (Å) and angles (deg) are given for (**7**) with the corresponding value for the free enediyne (**3**) in brackets: C1–C2 1.448(10) [1.414(5)], C1–C7 1.431(9) [1.437(3)], C2–C14 1.431(10) [1.437(3)], C7–C8 1.219(9) [1.187(4)], C14–C13 1.207(9) [1.187(4)]; C1–C2–C14 118.1(6) [117.04(14)], C2–C1–C7 116.8(6) [117.04(14)], C1–C7–C8 164.2(7) [166.4(3)], C2–C14–C13 166.5(6) [166.4(3)], C7–C8–C9 174.3(7) [174.7(3)], C12–C13–C14 174.9(6) [174.7(3)].

process for cycloaromatization. The increased yield of cycloaromatized product from substituted enediynes **10** and **11**, relative to unsubstituted **3**, is presumably related to steric inhibition of ruthenium coordination to the arene in **10** and **11**, which in turn shifts a partitioning between uncyclized and cyclized product toward the cyclized form.

Access to **3** and **7** permitted a determination of the effect that metal–ene coordination has on the rate of a Bergman cycloaromatization reaction. In nitromethane-*d*<sub>3</sub> (1,4-cyclohexadiene, 0.21 M), enediyne **3** (0.056 M) underwent a clean cycloaromatization to give **4** over the course of 18 days at 100 °C. In marked contrast, the ruthenium complex **7** was stable under essentially identical reaction conditions. Whereas **3** undergoes a photochemical Bergman cycloaromatization in the presence of 1,4-cyclohexadiene,<sup>12,13</sup> photolysis (Hanovia 450 W, 48 h) of **7** in CD<sub>2</sub>Cl<sub>2</sub> in the presence of 1,4-cyclohexadiene (0.25 M) failed to give an observable reaction by NMR spectroscopy.

The reluctance of **7** to undergo cycloaromatization (relative to **3**) is presumably related to decreased aromaticity in the incipient 1,4-diradical which would be generated from **7**. In the solid-state structure of **7** (Figure 1), the C8–C13 nonbonded distance of 3.32 Å is typical of 10-membered ring enediynes<sup>14</sup> and similar to the 3.27 Å distance observed in the solid-state structure of **3**.<sup>15</sup> Within experimental uncertainty, there is little difference in bond angles and distances between **3** and **7** (Figure 1, caption).

Efforts are currently underway to develop a catalytic version of this novel cycloaromatization chemistry, and extend the work reported here to nonaromatic acyclic enediyne and simple diene-yne substrates.

**Acknowledgment.** This work was supported by the National Science Foundation (CHE-9970480) and the University of California Cancer Research Coordinating Committee funds.

**Supporting Information Available:** Characterization data for compounds **7**, **9**, **12**, **13**, the **15/16** mixture, and **17**; tables of crystallographic data for **3**, **7**, and **9** (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA005514C