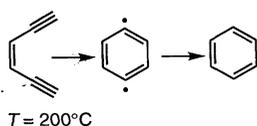


# Controlled Acceleration and Inhibition of Bergman Cyclization by Metal Chlorides

Benjamin P. Warner, Susan P. Millar, Richard D. Broene, Stephen L. Buchwald\*

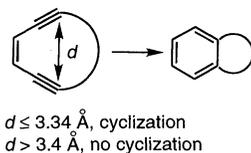
The Bergman cyclization has been the subject of renewed interest with the discovery of naturally occurring enediyne-based antitumor agents that cleave DNA by means of an aromatic diradical. These natural substrates have a means to trigger this cycloaromatization process. Control of this reaction by substrate modification would allow aromatic diradicals to be generated selectively. In the studies presented here it is disclosed that the Bergman cyclization of 1,2-bis(diphenyl phosphinoethynyl)benzene was accelerated by a factor of >30,000 by the addition of palladium(II) chloride or platinum(II) chloride and was inhibited by the addition of mercury(II) chloride.

We recently became interested in developing compounds in which conformational changes induced by host-guest or metal-ligand interactions lead to chemical or physical changes in the material (Fig. 1). One class of compounds known to respond to slight changes in geometry are the enediynes, which undergo Bergman cyclization to the 1,4-benzene diradicals (as shown in Scheme 1) (1). The rate of this reaction



Scheme 1

depends strongly on the distance between the alkyne termini (Scheme 2) (2). Several naturally occurring (3) and designed



Scheme 2

(4–7) compounds with antitumor properties contain the enediyne moiety, which has stimulated renewed interest in Bergman cyclization.

The synthesis of these enediynes has yielded several insights into the requirements for Bergman cyclization. Most prominent among these is the correlation of the distance between the alkyne termini (distance  $d$  in Scheme 2) with the facility of an enediyne to undergo cyclization. Enediynes in which  $d < 3.34 \text{ \AA}$  cyclize, whereas cyclizations are not observed in those in which

$d > 3.4 \text{ \AA}$  (2, 8). Enediynes whose alkyne termini are separated by distances of less than  $3.2 \text{ \AA}$  have not been isolated, presumably because of their extreme reactivity.

Enediyne antibiotics can trigger the formation of the reactive diradical (2). Several strategies to mimic this ability to control Bergman cyclization have been explored in order to design compounds of enhanced pharmacological utility. These include photochemical generation (9) and photochemical manipulation (5) of the enediyne, acid-base control of the enediyne conformation (5), and complexation of metals by a crown ether-functionalized enediyne (10).

As part of our investigation into viable means for controlling the reactivity of enediynes, we identified five attributes for a designed enediyne that would facilitate its exploitation in biological systems. The molecule must be (i) stable enough to store, (ii) compatible with biological systems, (iii) able to bind to protein or nucleic acid fragments, (iv) easy to synthesize, and (v) able to cyclize readily at ambient temperatures. A candidate that meets these criteria is an acyclic enediyne capable of chelating a metal. Upon complexation, the termini of the alkynes are brought close enough together to effect cyclization. Given the wide choice of size among the metals, the size of the ring (and thus the speed of cyclization)

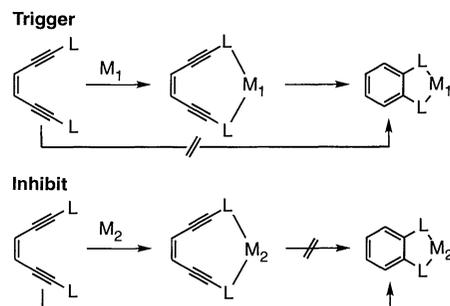


Fig. 1. Triggering and inhibition of Bergman cyclization; M, metal; L, ligand.

should be controllable. A metal complex compatible with biological conditions, such as *cis*-platin (11), could be used for triggering Bergman cyclization.

Compound 1 (Fig. 2) was shown to meet these five requirements. It is indefinitely stable under an inert atmosphere, is stable in air for several hours with no sign of decomposition, and shows no change on heating at  $95^\circ\text{C}$  for 20 days. It is readily synthesized in two steps from commercially available materials (12). Moreover, its simplicity should ease the preparation of analogs containing a recognition element. When complexed to a suitable metal, 1 undergoes a very rapid Bergman cyclization to the corresponding naphthalene.

We began our investigation of the Bergman cyclization of 1 by modeling the phosphine-metal complexes derived from coordination of 1 to  $\text{HgCl}_2$ ,  $\text{PdCl}_2$ , and  $\text{PtCl}_2$ , as well as the free ligand (13). Both complexes 2a and 2b (Fig. 2) had  $d = 3.3 \text{ \AA}$ , and 2c had  $d = 3.4 \text{ \AA}$ . These distances suggested that 2a and 2b should cyclize at room temperature, whereas 2c should not cyclize, even at elevated temperatures (2). We confirmed these hypotheses by generating these complexes (14) and investigating their properties by both nuclear magnetic resonance (NMR) spectroscopy and differential scanning calorimetry (DSC).

Grubbs and Kratz (15) and König and Rütters (10) applied DSC in the investigation of enediyne cyclizations and quantitatively measured the energy evolved in a reaction and determined its reversibility. Exothermic peaks (free energy,  $\Delta G = 24$  to  $39 \text{ kcal mol}^{-1}$ ) attributed to a Bergman cyclization to polymeric aromatic material (16) were observed for all enediynes studied. Subsequent reanalyses of the samples showed no further peaks, indicating that the reaction was irreversible. Compounds 1, 1· $\text{PdCl}_2$  (a 1:1 mixture of 1 and  $\text{PdCl}_2$ ) and 1· $\text{PtCl}_2$  displayed similar behavior by DSC (17). The free ligand 1 showed an irreversible exothermic ( $\Delta G = 46 \text{ kcal}$

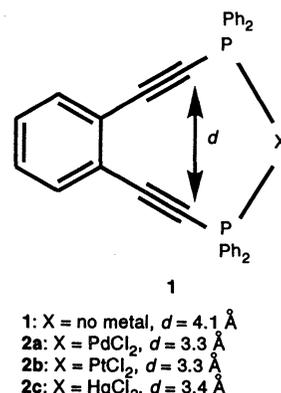
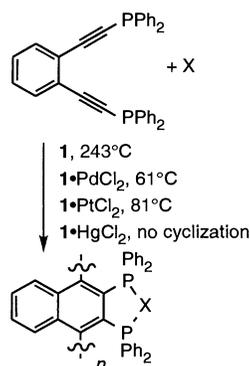


Fig. 2. Structures of compounds 1, 2a, 2b, and 2c.

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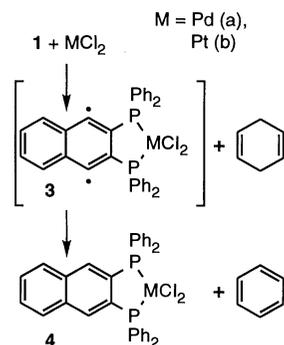
mol<sup>-1</sup>, cyclization temperature = 243°C) peak attributable to Bergman cyclization (Scheme 3). The temperature required for



Scheme 3

the cyclization of **1** is similar to the values reported (286° to 317°C) for other benzannulated, acyclic enediynes (15). Complex **1**•PdCl<sub>2</sub> showed an irreversible exothermic (26 kcal mol<sup>-1</sup>, 61°C) peak also attributable to cyclization, as did **1**•PtCl<sub>2</sub> (51 kcal mol<sup>-1</sup>, 81°C). The temperature required for the cyclization of **1** was lowered by 182°C upon complexation to PdCl<sub>2</sub> and by 162°C upon complexation to PtCl<sub>2</sub>. In contrast, **1**•HgCl<sub>2</sub> showed a phase change at 226°C, but no evidence for cyclization was seen at temperatures of up to 450°C, which implied that complexation to HgCl<sub>2</sub> prevents the Bergman cyclization of **1**. These results support our hypothesis that the cyclization of **1** can be accelerated or slowed by judicious choice of the metal added (Scheme 3).

The cyclizations of **1**•MCl<sub>2</sub> (M = Pd, Pt) were carried out with 1,4-cyclohexadiene (CHD) as a trapping agent (18) to yield **4** (19) (Scheme 4). We studied the cycliza-



Scheme 4

tion of **1**•PdCl<sub>2</sub> extensively to determine the rate, the mechanism, and the possibility that the conversion of **1**•PdCl<sub>2</sub> to **4a** occurred through a Bergman-type 1,4-aromatic diradical. We monitored the cyclization reaction by <sup>31</sup>P NMR to determine the reaction order and activation parameters.

The <sup>31</sup>P NMR spectra of solutions of **1**•PdCl<sub>2</sub> showed two species, which were assigned as the monomeric **2a** and the dimeric **5** (20) (Fig. 3). These species were found to be in equilibrium (equilibrium constant, *K*, of 0.0058 M) on the basis of a <sup>31</sup>P NMR saturation transfer experiment (21). In order to confirm this, we added 1 equivalent of 1,2-bis(diphenylphosphino)ethane (dppe) to the reaction mixture. Because dppe is a better ligand for PdCl<sub>2</sub> than **1**, this caused the reformation of **1** and the generation of (dppe)PdCl<sub>2</sub>. Addition of either dppe or Ph<sub>3</sub>P (Ph, phenyl) prevented the cyclization of **2a** to **4a**; these compounds successfully compete with **1** for PdCl<sub>2</sub>. This provides evidence for the dependence of cyclization on the formation of a complex between Pd and **1**.

We followed the disappearance of the dimer **5** by <sup>31</sup>P NMR to determine the rate of the reaction. The soluble PdCl<sub>2</sub> source, (CH<sub>3</sub>CN)<sub>2</sub>PdCl<sub>2</sub>, and **1** were mixed in equimolar amounts, with CHD added as a trapping agent (18), in CD<sub>2</sub>Cl<sub>2</sub> (Scheme 4, M = Pd). The rate was found to be 1/2 order in **1**•PdCl<sub>2</sub> and essentially zero order in CHD (Fig. 4). The rate constant was 0.0024 mmol<sup>1/2</sup> min<sup>-1</sup>. The empirical rate law is

$$\text{rate (mmol min}^{-1}\text{)} = 0.0024 (\text{mmol}^{1/2} \text{ min}^{-1}) [\mathbf{1}\cdot\text{PdCl}_2]^{1/2} \quad (1)$$

We also ran the cyclization reaction using deuterated 1,2,3,4,5,6-*d*<sub>6</sub>-cyclohexadiene (22) as the trapping agent. The ratio of rates of trapping diradical **3a** by hydrogen or deuterium (*k*<sub>H</sub>/*k*<sub>D</sub>), which is equal to the ratio of *d*<sub>0</sub> and *d*<sub>2</sub> **4a**, was 4.5 ± 0.2. This result is in agreement with studies by Bergman and co-workers who found *k*<sub>H</sub>/*k*<sub>D</sub> = 4.3 for the cyclization of Z-4,5-diethynyl-4-octene to 1,2-dipropylbenzene (18).

On the basis of these data, we propose that the mixture of **1** and PdCl<sub>2</sub> forms a dimeric species **5** (20) that disproportionates to a monomeric species **2a** and undergoes cyclization to the diradical **3a** in a rate-limiting step. The diradical is then rapidly trapped by CHD to form **4a** (18) (Fig. 3).

If we assume that the diradical **3a** is at steady state, the calculated rate law for this process is

$$\text{rate} = k_3 k_5 [\text{CHD}] (K[\mathbf{5}])^{1/2} / (k_5 [\text{CHD}] + k_4) \quad (2)$$

If *k*<sub>5</sub>[CHD] is much larger than *k*<sub>4</sub>, formation of the diradical (*k*<sub>3</sub>) becomes rate-limiting, and Eq. 2 reduces to Eq. 3, which is identical to Eq. 1:

$$\text{rate} = k_3 (K[\mathbf{5}])^{1/2} \quad (3)$$

Substitution of known values for the rate, *K*, and [**5**] yields the value of 0.041 ml min<sup>-1</sup> for *k*<sub>3</sub>.

The rate of cyclization of **1**•PtCl<sub>2</sub> was 2.7 times that of **1**•PdCl<sub>2</sub>, as determined by <sup>1</sup>H NMR, although **1**•PdCl<sub>2</sub> underwent cyclization at a lower temperature than **1**•PtCl<sub>2</sub> as monitored by DSC. However, the DSC-monitored reaction was run in the solid state, whereas the NMR-monitored reaction was run in solution. Further, the reactions run in solution used CHD as a radical trapping reagent (18), whereas the solid-state reactions used yielded polymeric material (16). These different conditions prevent the exact correlation of onset temperature and rate of cyclization in solution.

The rate of the Pd-promoted cyclization compares favorably to that of other enediynes that have been studied (2, 8, 23). The reaction has a half-life of 42 min ([**1**•PdCl<sub>2</sub>] = 0.025 M, [CHD] = 0.125 M, 35°C), which is an acceleration of at least

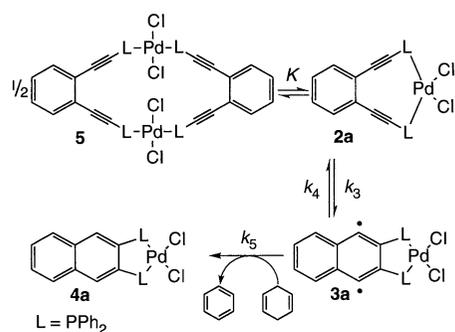


Fig. 3. Reaction of **1** and PdCl<sub>2</sub> produces **5**, which is in equilibrium with **2a**. Intermediate **2a** undergoes cyclization to form **3a** and, subsequently, **4a**.

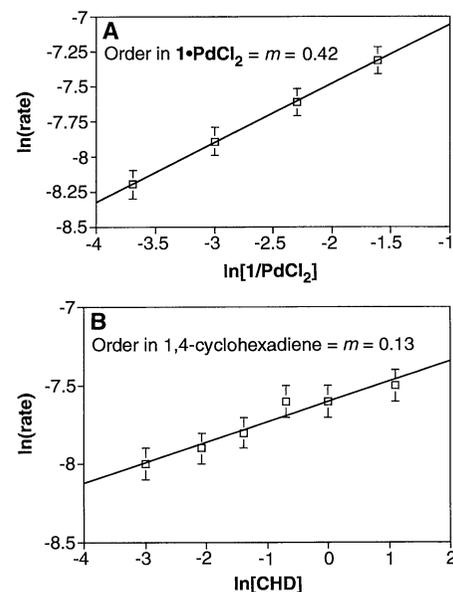
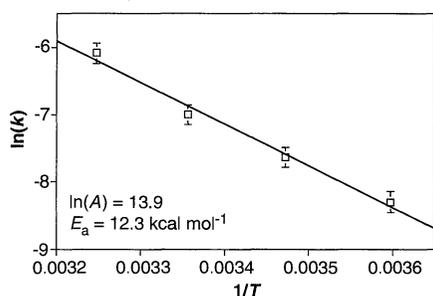


Fig. 4. Plot of ln(rate) versus ln[reagent] for cyclization of **1**•PdCl<sub>2</sub> to **4a**. The slope of the line is reaction order in (A) **1**•PdCl<sub>2</sub> and (B) CHD. Each point is an average of two or more runs.



**Fig. 5.** Arrhenius plot of the cyclization of **1-PdCl<sub>2</sub>** to **4a**. Each point is an average of two or more runs.

30,000 times over the unpromoted reaction (24). The activation parameters for this process ( $[1\text{-PdCl}_2] = 0.025\text{ M}$ ,  $[\text{CHD}] = 0.5\text{ M}$ , temperature  $T = 278\text{ to }308\text{ K}$ ) are activation energy  $E_a = 12.3\text{ kcal mol}^{-1}$  and  $\ln(A) = 13.9$  (Fig. 5), reflecting the ease of cyclization under these conditions (25).

We have developed an enediyne-based diphosphine which upon coordination of **1** to palladium or platinum dichloride undergoes a Bergman cyclization at an enormously enhanced rate. In contrast, complexation of **1** to mercuric chloride prevents this cyclization. This system meets the criteria of speed, compatibility, stability, and ease of synthesis presented above. Under appropriate conditions, including in the presence of palladium or platinum dichloride, **1** undergoes rapid cyclization at low temperatures.

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- 3285, 3053, 3002, 2954, 2278, 2161, 1954, 1890, 1811, 1752, 1585, 1477, 1434, 1327, 1305, 1274, 1247, 1230, 1204, 1182, 1158, 1097, 1068, 1026, 999, 951, 912, 873, 842, 809, 739, 695, 642, and 632 cm<sup>-1</sup>. Analysis: calculated for C<sub>34</sub>H<sub>24</sub>P<sub>2</sub>: C, 82.58%; H, 4.89%; found: C, 82.48%; H, 5.09%.
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- Characterization of **4a**: Isolated yield, 92%. Melting point (324°C (decomposes)). <sup>1</sup>H NMR (300 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$  7.46 (t,  $J = 6.7\text{ Hz}$ , 8 H), 7.54 (d,  $J = 7.5\text{ Hz}$ , 4 H), 7.66 (dd,  $J = 3.2\text{ Hz}$ , 6.2 Hz, 2 H), 7.78 (dd,  $J = 7.5\text{ Hz}$ , 12.4 Hz, 8 H), 7.89 (dd,  $J = 3.2\text{ Hz}$ , 6.2 Hz, 2 H), and 8.08 (d,  $J = 11\text{ Hz}$ , 2 H). <sup>13</sup>C NMR (75 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$  134.43, 134.37, 134.30, 132.35, 130.06, 129.34, 129.24, 129.18, and 129.11. <sup>31</sup>P NMR (121 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$  62.05. Analysis: calculated for C<sub>34</sub>H<sub>26</sub>Cl<sub>2</sub>P<sub>2</sub>Pd: C, 60.60%; H, 3.89%; found: C, 60.64%; H, 3.99%. Characterization of **4b**: Isolated yield, 75%. Melting point >400°C (decomposes). <sup>1</sup>H NMR (300 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$  7.42 to 7.50 (m, 8 H), 7.50 to 7.55 (m, 4 H), 7.66 (dd,  $J = 3.2\text{ Hz}$ , 6.2 Hz, 2 H), 7.75 to 7.82 (m, 8 H), 7.89 (dd,  $J = 3.4\text{ Hz}$ , 6.4 Hz, 2 H), and

- 8.11 (d,  $J = 12.2\text{ Hz}$ , 2 H). <sup>13</sup>C NMR (75 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$  134.54, 134.47, 134.39, 132.45, 130.20, 129.52, 129.42, 129.34, and 129.27. <sup>31</sup>P NMR (121 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$  39.6 (d,  $J_{\text{P-Pt}} = 3596\text{ Hz}$ ). Analysis: calculated for C<sub>34</sub>H<sub>26</sub>Cl<sub>2</sub>P<sub>2</sub>Pt: C, 53.56%; H, 3.44%; found: C, 53.85%; H, 3.62%.
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- Activation energies for some other Bergman cyclizations studied range from 27.4 kcal mol<sup>-1</sup> (20) for acyclic enediynes to 19.4 kcal mol<sup>-1</sup> (7) for a 10-membered ring. Most relevant is the value of  $E_a = 25.1\text{ kcal mol}^{-1}$  determined for the cycloaromatization of 1,2-bis(ethynyl)benzene: J. W. Grissom, T. L. Calkins, H. A. McMillen, Y. Jiang, *J. Org. Chem.* **59**, 5833 (1994).
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## Confinement-Induced Phase Transitions in Simple Liquids

Jacob Klein and Eugenia Kumacheva

The liquid-to-solid transition of a simple model liquid confined between two surfaces was studied as a function of surface separation. From large surface separations (more than 1000 angstroms) down to a separation corresponding to seven molecular layers, the confined films displayed a liquid-like shear viscosity. When the surface separation was further decreased by a single molecular spacing, the films underwent an abrupt, reversible transition to a solid. At the transition, the rigidity of the confined films (quantified in terms of an "effective viscosity") increased reversibly by at least seven orders of magnitude.

The properties of fluids confined to nanoscopic pores or films differ greatly from the properties of fluids in the bulk. For example, liquid lubricants solidify on being compressed to ultrathin layers (1), gases trapped in nanometer-sized pores order into crystalline arrays (2), and simple liquids confined between solid surfaces undergo layering adjacent to each surface (3, 4). The behavior of such films is of central importance for understanding tribology, adhesion and wear properties (5), the wetting and dewetting of surfaces, and the microfluidity of biological membranes (6); insight into the properties of such films is also important for understanding the rigidity and flow behavior of granular materials (7), ceramics (8), and

advanced composites (9), in which deformation occurs by means of the shearing of thin interfacial layers at grain or phase boundaries. However, at a more fundamental level, the interplay at increasing confinement of the dynamics, thermodynamics, and the molecular structure of the fluids, and their commensurability and interactions with the confining walls, is not yet well understood (10, 11).

Measurements of the dynamic properties of simple liquids suggest that these liquids retain their bulk viscosity for films thicker than approximately 10 molecular diameters (12–14). At the other extreme, highly compressed liquid films confined to one to three molecular layers between smooth solid surfaces display solidlike features, evidenced by a finite yield stress (15–17). Computer simulations and theoretical investigations have

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