Determination of the Activation Parameters for the Bergman Cyclization of Aromatic Enediynes

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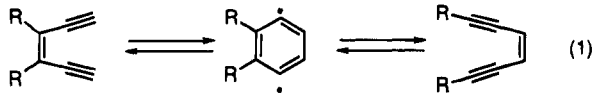
Introduction

Early investigations in enediyne chemistry were fueled by the novel thermal isomerization of these compounds to aromatic 1,4-biradicals.[1] Recently, the interest in enediyne chemistry has increased due to the presence of this moiety in several antitumor agents.[2] Our investigations have focused on the trapping of the 1,4-aromatic biradical with pendant radical acceptors, thus leading to the synthesis of multicyclic systems.[3] An earlier publication by our research group outlined a kinetic and mechanistic investigation of the tandem enediyne–radical cyclization.[4] Herein is reported an expansion on the previous publication which includes additional kinetics including the determination of the activation energies for the Bergman cyclization of several aromatic enediynes.

In the early 1970's, Bergman and co-workers postulated that the parent *cis*-hex-3-ene-1,5-diyne (**1**), upon thermolysis, will undergo a symmetry-allowed rearrangement to the reactive intermediate 1,4-didehydrobenzene (**2**), which can collapse to starting material or the rearrangement product **3** (eq 1).[1a] From the thermolysis



(1)

1 R = H
4 R = *n*-Propyl

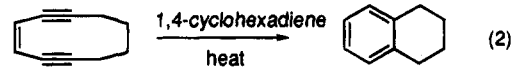
2

3 R = H
5 R = *n*-Propyl

reaction of **1** at 200 °C, Bergman estimated the activation energy to be ≈32 kcal/mol. Due to the difficulty in handling enediyne **1**, Bergman and co-workers were unable to complete careful kinetic experiments to determine an accurate activation energy.

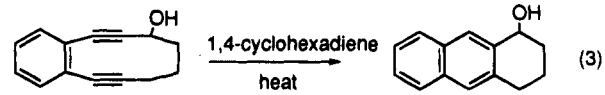
Bergman and co-workers were, however, able to determine the energy of activation for the cyclization of enediyne **4** (eq 1),[1d] of which the activation energy for the Bergman cyclization should be similar to **1**. First-order plots of kinetic data for the cyclization of **4** monitored for 2–3 half-lives over a range of 34 °C gave an Arrhenius relationship affording $E_a = 27.4 \pm 0.5$ kcal/mol, a value substantially smaller than that originally calculated by Bergman for the thermal cyclization of **1**. It was also noted that the cyclization of **4** to **2** occurs more readily than the conversion of **5** to **2**.

Nicolaou has shown that by tethering the two acetylenes into a 10-membered ring, there is a lowering of the activation energy for the Bergman cyclization (eq 2).[5]



(2)

Kinetic data for this cyclization showed an Arrhenius relationship affording $E_a = 23.8 \pm 0.04$ kcal/mol. Boger has also carried out studies on an aromatic enediyne analogous to the Nicolaou substrate (eq 3) and deter-



(3)

mined that the Arrhenius relationship is $E_a = 19.4$ kcal/mol,[6] a value lower than that determined for Nicolaou's cyclic nonaromatic enediyne.[5] In contrast to Boger's work, other studies by Just,[7] Semmelhack,[8] and Nicolaou[9] suggest qualitatively that the cyclic aromatic enediynes cyclize more slowly than the nonaromatic analogues.

These experiments by Boger and Nicolaou outline the activation parameters necessary for the Bergman cyclization of a cyclic aromatic and nonaromatic enediyne. Bergman's work measured the energy of activation of the cyclization of an acyclic nonaromatic enediyne **4**; however, the energy of activation of the cyclization of the related enediyne **5** was not quantitated. There has not been any determination of the activation parameters for the cyclization of an acyclic aromatic enediyne, nor has the effect of acetylene substitution on the rate of cyclization been quantitatively studied.

In our previous publication, it was reported that the tandem enediyne–radical cyclization of aromatic substrates containing electronically different olefin acceptors proceeds through the formation of a distinct 1,4-biradical intermediate in the rate-determining step, followed by a rapid 5-*exo* radical cyclization.[4] The reactions that were investigated followed first-order kinetics with rate constants of $\approx 10^{-4}$ s^{-1} at 191 °C.[10,11] To determine the rate of cyclization at different temperatures and the respective activation energies (E_a), kinetic experiments were performed on various acyclic tandem aromatic enediyne–radical cyclization substrates. The purpose of the present study was to determine how pronounced an effect the substitution on the acetylenes would have on the rate of cyclization and whether the E_a for the cyclization of acyclic aromatic enediynes would be significantly differ-

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(2) For a general overview on the enediyne antibiotics see: (a) Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387. (b) Nicolaou, K. C.; Smith, A. L. *Acc. Chem. Res.* **1992**, *25*, 497.

(3) (a) Grissom, J. W.; Calkins, T. L.; Egan, M. *J. Am. Chem. Soc.* **1993**, *115*, 11744. (b) Grissom, J. W.; Calkins, T. L. *Tetrahedron Lett.* **1992**, *33*, 2315. (c) Grissom, J. W.; Calkins, T. L.: McMillen, H. A. *J. Org. Chem*, **1993**, *58*, 6556. (d) Grissom, J. W.; Calkins, T. L.; Huang, D. *Tetrahedron* **1994**, *50*, 4635. (e) Grissom, J. W.; Klingberg, D. *J. Org. Chem.* **1993**, *58*, 6559.

(4) Grissom, J. W.; Calkins, T. L. *J. Org. Chem.* **1993**, *58*, 5422.

(5) (a) Nicolaou, K. C.; Ogawa, Y.; Zuccarello, G.; Kataoka, H. *J. Am. Chem. Soc.* **1988**, *110*, 7247. (b) Nicolaou, K. C.; Zuccarello, G.; Ogawa, Y.; Schweiger, E. J.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 4866.

(6) Boger, D. L.; Zhou, J. *J. Org. Chem.* **1993**, *58*, 3018.

(7) Just, G.; Singh, R. *Tetrahedron Lett.* **1990**, *31*, 185.

(8) Semmelhack, M. F.; Neu, T.; Foubelo, F. *Tetrahedron Lett.* **1992**, *33*, 3277.

(9) Nicolaou, K. C.; Liu, A.; Zheng, Z.; McComb, S. *J. Am. Chem. Soc.* **1992**, *114*, 9279.

(10) We previously reported that the rate did not change when either the enediyne or 1,4-CHD concentration was varied (ref 4).

(11) The experimental errors determined over several runs were negligible. Therefore, the errors reported represent errors in fitting to the first-order curve.

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Table 1. Rate Constants for the Cyclization of 6 (0.01 M) with 1,4-Cyclohexadiene (1 M)[a]

entry	T (°C)	k (s^{-1})	error (s^{-1})[11]
1	152	2.2×10^{-4}	9.1×10^{-6}
2	166	4.9×10^{-4}	3.2×10^{-5}
3	177	1.1×10^{-3}	5.7×10^{-5}
4	188	2.2×10^{-3}	1.5×10^{-4}
5	190	2.4×10^{-3}	9.5×10^{-5}

[a] $E_a = 25.1 \pm 0.8$ kcal/mol.

Table 2. Rate Constants for the Cyclization of 8 (0.0089 M) with 1,4-Cyclohexadiene (1 M)[a]

entry	T (°C)	k (s^{-1})	error (s^{-1})[11]
2	167	9.4×10^{-5}	5.3×10^{-6}
3	180	2.3×10^{-4}	4.2×10^{-6}
4	192	5.5×10^{-4}	6.0×10^{-6}
5	199	7.7×10^{-4}	1.9×10^{-6}

[a] $E_a = 28.1 \pm 0.8$ kcal/mol.

Table 3. Rate Constants for the Cyclization of 10 (0.0089 M) with 1,4-Cyclohexadiene (1 M)[a]

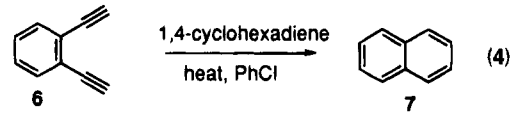
entry	T (°C)	k (s^{-1})	error (s^{-1})
1	235	9.5×10^{-5}	3.5×10^{-6}
2	247	2.2×10^{-4}	6.7×10^{-6}
3	253	3.1×10^{-4}	8.8×10^{-6}
4	263	5.7×10^{-4}	1.5×10^{-5}

[a] $E_a = 34.0 \pm 0.3$ kcal/mol.

ent from the nonaromatic enediynes. The rates were measured over a 30–50 °C temperature range, and the reactions were monitored for 2–3 half-lives.

Results and Discussion

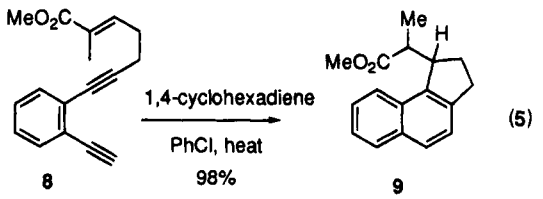
Enediyne **6** which affords **7** (eq 4)[4]



(4)

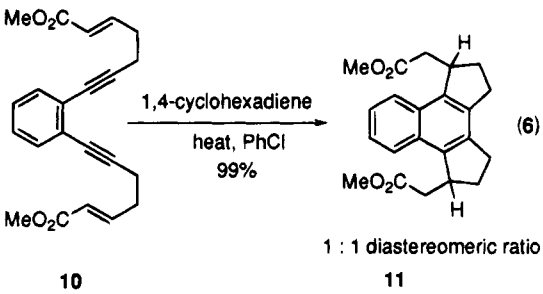
showed first-order kinetics over a 38 °C temperature range. The respective rate constants for enediyne **6** are summarized in Table 1. First-order plots of kinetic data for the cyclization of **6** monitored for 2–3 half-lives gave an Arrhenius relationship affording $E_a = 25.1 \pm 0.8$ kcal/mol. This value is slightly lower than the $E_a = 27.4 \pm 0.5$ kcal/mol calculated for **4** by Bergman and co-workers.[1] From this similarity, it can be inferred that the E_a for the acyclic Bergman cyclization of an aromatic enediyne is not substantially different from the E_a for a nonaromatic enediyne. Apparently, the incorporation of the aromatic ring has a minimal effect on the rate of the Bergman cyclization.

Incorporation of one acetylenic substituent on the aromatic enediyne caused a small decrease in the rate of the Bergman cyclization. Since the rate of the tandem enediyne–radical cyclization is determined only by the rate of the enediyne cyclization, and not the 5-*exo* radical cyclization, the presence of the olefinic tether would not be expected to affect the overall rate of the reaction.[4] The rate constants were determined over a 48 °C temperature range and likewise were determined to be first order for the thermolysis of **8** which afforded **9** in 98% yield as a 3:1 mixture of diastereomers.[3a] Variations in the concentration of substrate or 1,4-CHD did not affect the rate of the reaction.[4] The rate constants for the cyclization of compound **8** are summarized in Table 2. First-order plots of kinetic data for the cyclization of **8** monitored for 2–3 half-lives gave an Arrhenius relationship affording $E_a = 28.1 \pm 0.8$ kcal/mol. From this result, it can be concluded that the incorporation of one acetylenic substituent has a moderate effect of slowing the rate of the Bergman cyclization.



(5)

The addition of a second acetylenic tether had a substantial effect on the rate of the Bergman cyclization. The rate constants were determined over a 30 °C temperature range for **10** which affords **11** as a 1:1 mixture of diastereomers in 99% yield (eq 5).[3a] In accord



(6)

with the previous two examples, the cyclization of **10** showed first-order kinetics, but a substantially slower rate. The rate constants for the thermolysis of **10** are summarized in Table 3, and the rate constants for **10** showed an Arrhenius relationship affording $E_a = 34.0 \pm 0.3$ kcal/mol. This activation energy is ≈6 kcal/mol higher than the monotethered analog.

Nicolaou has proposed that the energy of activation for the Bergman cyclization is dependent on the distance between the acetylenes.[5] There appears to be agreement that this explanation does not explain all of the observed data. A second explanation proposed by Snyder postulates that the ease of cyclization of any enediyne is dependent upon the differential molecular strain between the ground state and the transition state.[12] It is unclear whether either theory can be applied to acyclic enediynes. In any case it is reasonable to assume steric factors should affect the rate of these cyclizations, and our results suggest that steric interactions between the acetylenic substituents play an important role in determining how facile the enediyne cyclization will be. The acetylenic substituents can either push the acetylenes apart and/or distort the enediyne system from planarity; both effects will increase the energy of activation of the enediyne cyclization. The effect is most pronounced for the substrate **10** with two acetylenic substituents. A similar effect was noted by Bergman in that enediyne **5** with two acetylenic substituents was also reluctant to undergo cyclization.[1d]

Conclusion

The effect of acetylene substitution on the rate of cyclization of acyclic aromatic enediynes has been deter-

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mined by kinetic experiments. A direct comparison between an acyclic nonaromatic enediyne **4** and an acyclic aromatic enediyne **6** both containing unsubstituted acetylenes indicates that the rate of the Bergman cyclization is not significantly different. Therefore, it can be concluded that there exists little difference in the activation parameters for the cyclization of the acyclic aromatic and nonaromatic enediynes and that the acetylene substitution is the primary determining factor in the rate of the enediyne cyclization. One acetylenic substituent has a small effect of slowing the rate of enediyne cyclization while the addition of a second acetylenic substituent increases the activation energy by 9 kcal/mol.

Experimental Section

All kinetic data were obtained by analytical GC on a Shimadzu GC-14A using a CR-601 integrator. The analysis was done using a 0.54 SE-54 wide bore capillary column with helium as the carrier gas. Naphthalene or anthracene was used as the internal standard in all studies. The experiments were all performed in chlorobenzene purified by passing through basic alumina. 1,4-Cyclohexadiene was purchased from Jannsen Chemica and used without further purification. The GC data was analyzed using Enzfitter on an IBM PC. The experimental procedures for the preparative scale cyclizations of **6**, **8**, and **10** to obtain yields are described in earlier papers.[3a,b,4]

Kinetics Study of 6. To a predried 5 mL volumetric flask was added anthracene (0.0055 g), **6** (≈0.005 g), and 1,4-cyclohexadiene (0.470 mL). The volumetric flask was filled to the 5 mL mark with anhydrous chlorobenzene. The reaction solution was well mixed by shaking and analyzed by analytical gas chromatography. The reaction solution was determined to be 0.013 M in enediyne with respect to the integration of the internal standard. Then 10 μL aliquots of the reaction solution were placed in capillary melting point tubes and subsequently sealed under high vacuum and oxygen torch with only enough empty space for liquid expansion. Then five different kinetic experiments at 152, 166, 177, 188, and 190 °C were conducted and monitored for 2–3 half-lives.[4] The thermolyzed tubes were analyzed by analytical gas chromatography with the following time program. Initial temperature = 70 °C, 5 °C/min until 220 °C and then 20 °C/min to 250 °C.

Kinetics Study of 8. To a predried 5 mL volumetric flask was added naphthalene (0.0017 g), **8** (≈0.010 g), and 1,4-cyclohexadiene (0.470 mL). The volumetric flask was filled to the 5 mL mark with anhydrous chlorobenzene giving a reaction solution of 0.0089 M in enediyne as determined by analytical gas chromatography. Then four different kinetic experiments at 167, 180, 192, and 199 °C were conducted as described for **6** and monitored for 2–3 half-lives. GC analysis was carried out with the following time program. Initial temperature = 100 °C for 3 min, then 20 °C/min until 150 °C, and then 3 °C/min to 250 °C.

Kinetics Study of 10. To a predried 5 mL volumetric flask was added naphthalene (0.0039 g), **10** (≈0.025 g), and 1,4-cyclohexadiene (0.470 mL). The volumetric flask was filled to the 5 mL mark with anhydrous chlorobenzene giving a reaction solution of 0.0089 M in enediyne as determined by analytical gas chromatography. Then four different kinetic experiments at 235, 247, 253, and 263 °C were conducted and monitored for 2–3 half-lives. GC analysis was carried out with the following time program. Initial temperature = 100 °C for 3 min, then 25 °C/min until 275 °C, and then hold for 10 min.

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Supplementary Material Available: Graphs of Arrhenius plots and tables of kinetic data for **6**, **8**, and **10** at various temperatures (15 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.