

Tuning Rate of the Bergman Cyclization of Benzannelated Eneidyne with Ortho Substituents

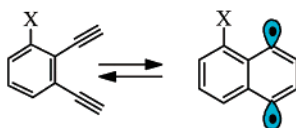
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ABSTRACT

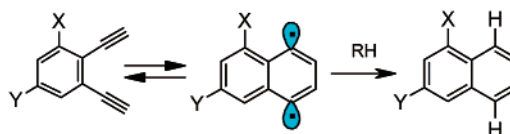


The Bergman cyclization of benzannelated enediynes is highly sensitive to ortho substitution. This finding opens possibilities for the rational design of conformer-specific and pH-dependent DNA-cleaving agents.

The thermal cyclization of (Z)-enediynes (the Bergman cyclization)¹ has a number of practical applications in the design of DNA-cleaving agents,² the development of polymeric materials with enhanced thermal properties,³ and synthesis of polycyclic compounds.⁴ Introduction of functional groups in benzannelated enediynes can provide a straightforward and synthetically viable way to control both the cyclization rate and molecular recognition of the enediyne moiety by DNA. Although the reactivity of heterocyclic enediynes⁵ shows considerable variation, only slight changes in the cyclization barrier were found for *para*-substituted benzene analogues.^{6,7} The developing radical centers are

orthogonal to the aromatic π -system, and therefore, the *para* substituents influence reactivity predominantly via the field effect.⁷ Electron-acceptor substituents are generally found to accelerate the cyclization as suggested by Koga and Morokuma⁸ because electron repulsion between the occupied *in-plane* alkyne π -orbitals should increase the cyclization barrier. A number of experimental results are consistent with this suggestion.⁹

Scheme 1. Bergman Cyclization of Benzannelated Eneidyne



The present study was prompted by our experimental finding of an *accelerating effect* by an *electron-donating* OMe group at the ortho position.¹⁰ Although the effect is subtle—2,3-diethynylanisole is only two times more reactive

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


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Table 1. Activation Barriers and Reaction Energies (kcal mol⁻¹) for Bergman Cyclizations of *ortho*- and *para*-Substituted 1,2-Diethynylbenzenes Calculated at the B3LYP/6-31G** Level; Data for *para*-Substituted Cases Given in Parentheses

R ^a							δE _R ^b	δE _{TS} ^b
	R _{C1...C6}	TS _{C1...C6}	ΔE ^{‡c}	ΔH [‡]	ΔG [‡]	ΔE _T		
H	4.212	1.924	31.3	30.1	32.0	11.03	0.00	0.00
F	4.208 (4.209)	1.926 (1.906)	31.3 (31.2)	30.1 (30.2)	32.0 (32.1)	10.8 (10.9)	0.72	0.82
Cl	4.129 (4.214)	1.930 (1.908)	31.3 (31.2)	29.9 (30.1)	31.7 (32.1)	10.0 (10.8)	1.68	1.77
Me	4.169 (4.218)	1.923 (1.914)	31.5 (31.3)	30.0 (30.9)	31.7 (31.1)	10.9 (10.9)	-0.11	0.09
NH ₂ (<i>np</i>)	4.108 (4.215)	1.897 (1.920)	31.3 (31.4)	30.3 (30.9)	32.2 (32.2)	10.4 (11.0)	1.91	1.87
NH ₂ (<i>p</i>)	4.229 (4.224)	1.908 (1.910)	32.3 (31.5)	31.2 (31.0)	32.9 (32.3)	12.4 (11.6)	-1.59	-0.83
CN	4.174 (4.240)	1.904 (1.919)	31.1 (31.0)	30.0 (30.0)	31.9 (31.9)	10.0 (10.6)	1.15	1.20
CF ₃	4.105 (4.207)	1.912 (1.912)	30.0 (31.0)	29.0 (30.0)	30.6 (31.9)	9.2 (10.3)	2.15	1.21
NO ₂	3.936 (4.196)	1.922 (1.909)	27.9 (30.9)	27.5 (29.9)	27.9 (31.8)	6.6 (10.4)	5.83	2.84
OH(<i>s</i>)	4.295 (4.222)	1.911 (1.912)	31.9 (31.3)	30.8 (30.3)	32.6 (32.2)	12.8 (11.0)	-2.80	-2.27
OH(<i>a</i>)	4.172 (4.210)	1.901 (1.908)	31.5 (31.4)	30.5 (30.3)	32.4 (32.2)	10.6 (11.4)	1.24	1.38
CHO(<i>s</i>)	4.022 (4.194)	1.942 (1.909)	27.7 (31.0)	26.8 (30.0)	28.8 (32.0)	6.8 (10.9)	3.88	0.54
CHO(<i>a</i>)	4.115 (4.206)	1.930 (1.913)	29.2 (31.1)	28.1 (30.0)	30.0 (32.0)	9.4 (10.4)	1.25	-0.60
OMe(<i>s, s</i>)	3.934 (4.219)	1.911 (1.913)	28.6 (31.4)	27.5 (30.4)	29.2 (32.3)	8.9 (10.8)	5.54	2.79
OMe(<i>s, e</i>)	3.900 (4.222)	1.924 (1.913)	27.7 (31.4)	27.1 (29.8)	26.9 (33.8)	8.0 (10.9)	4.92	1.21
OMe(<i>a, s</i>)	4.162 (4.214)	1.927 (1.906)	31.4 (31.5)	30.4 (30.4)	32.4 (32.4)	10.3 (11.9)	1.35	1.38
OMe(<i>a, e</i>)	4.150 (4.220)	1.900 (1.906)	31.6 (31.5)	30.5 (29.9)	32.4 (34.3)	10.4 (11.9)	1.51	1.61
NH ₃ ⁺ (<i>st</i>)	4.299 (4.188)	1.920 (1.902)	29.2 (30.3)	28.6 (29.6)	29.7 (31.3)	10.6 (9.6)	-3.73	-4.87
NH ₃ ⁺ (<i>ec</i>)	4.291 (4.193)	1.926 (1.906)	28.4 (30.2)	27.1 (29.3)	29.1 (31.1)	11.7 (9.2)	-4.95	-6.89

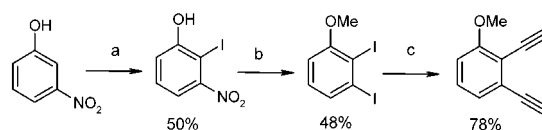
^a Planar and nonplanar conformers of NH₂, *syn* and *anti* conformers of OH, CHO, and OMe, and staggered and eclipsed conformations of OMe group were considered. ^b $\delta E = E_{ortho} - E_{para}$, difference in the absolute energies between ortho and para isomers. δE_R is the difference for the enedynes, and δE_{TS} is for transition states. ^c The ZPE correction is in the range of 0.2–0.8 kcal mol⁻¹.

than 1,2-diethynylbenzene at 170 °C¹¹ (Table 2, Supporting Information)—the direction of the change is unexpected. The accelerating influence of an electron-donor substituent clearly contradicts with the simple premise of the Koga–Morokuma hypothesis.

Intrigued by this result we undertook this theoretical analysis of the “proximity effect”¹² of ortho substituents in the Bergman cyclization. Below, we report our finding that the cyclization step is highly sensitive to the nature of ortho

substitution. We also evaluate specific mechanisms accounting for this phenomenon.

Scheme 2^a



^a Reagents and conditions: (a) (1) NaOH, Hg(OAc)₂, (2) KI, I₂; (b) (1) MeI, (2) N₂H₄, FeCl₃, (3) NaNO₂, KCl, KI; (c) Pd(PPh₃)₂, (1) Cu(I), HCCSiMe₃, (2) K₂CO₃, MeOH.

(7) Choy, N.; Kim, C.-S.; Ballesterio, C.; Argitis, L.; Diez, C.; Lichtenberg, F.; Shapiro, J.; Russell, K. C. *Tetrahedron Lett.* **2000**, *41*, 6995. Correlation of the reaction rate with Hammett σ_m value revealed a low sensitivity to substituents ($\rho = 0.654$). The Swain–Lupton model yielded a larger field parameter (0.662) than resonance parameter (0.227) indicating that conjugative effects in the out-of-plane π -system are of lesser importance than field effects.

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(9) Schmittel, M.; Kiau, S. *Chem. Lett.* **1995**, 953. Mayer, M. E.; Greiner, B. *Liebigs Ann. Chem.* **1992**, 855. Semmelhack, M. F.; Neu, T.; Foubelo, F. *J. Org. Chem.* **1994**, *59*, 5038. Nicolau, K. C.; Zuccarello, G.; Riemer, C.; Estevez, V. A.; Dai, W.-M. *J. Am. Chem. Soc.* **1992**, *114*, 7360.

(10) Synthesis of the enediyne is outlined in Figure 1. The key step involved Sonogashira coupling of TMS-acetylene with 3-OMe-1,2-diodobenzene in 78% yield. (See Supporting Information)

(11) We used the conditions of Grissom et al.:^{6b} 5.4 mg (0.034 mmol) of 1,2-diethynyl-3-methoxybenzene, 0.27 g (3.4 mmol) of 1,4-cyclohexadiene, and 4.7 mg (0.011 mmol) of tetraphenylnaphthalene internal standard were dissolved in 10 mL of chlorobenzene. Next, 50- μ L aliquots were sealed in thin capillaries (at the height where no dead volume was observed) after freeze–pump–thaw degassing and placed in an oil bath, the temperature being maintained at 170 °C with a “Temp-O-Trol” temperature controller (± 0.2 °C). The range of reaction times corresponded to 2–3 half-lives. The reaction mixtures were diluted with hexane and analyzed by analytical HPLC. The cyclization of 1,2-diethynylbenzene was studied under the same conditions (see Supporting Information). Importantly, the presence of an ortho substituent did not decrease the efficiency of the Bergman cyclization

All geometries were computed^{13,14} using either the restricted (reactant) or broken-spin unrestricted (TS and diradical product)¹⁵ B3LYP/6-31G** method which has been shown to provide reasonable accuracy for the Bergman cyclization.^{16,17} The computational results are summarized in Table 1.

In agreement with the experimental results of Russell and co-workers,⁷ the influence of para substituents on the cyclization is small. The activation energies for the neutral

as indicated by the yield of OMe-naphthalene (67%). The yield of naphthalene in the cyclization of 1,2-diethynylbenzene was 73%. Products formed by recombination of naphthyl and cyclohexadienyl radicals constitute the rest of the reaction mixtures.

(12) Charton, M. *Prog. Phys. Org. Chem.* **1971**, *8*, 235.

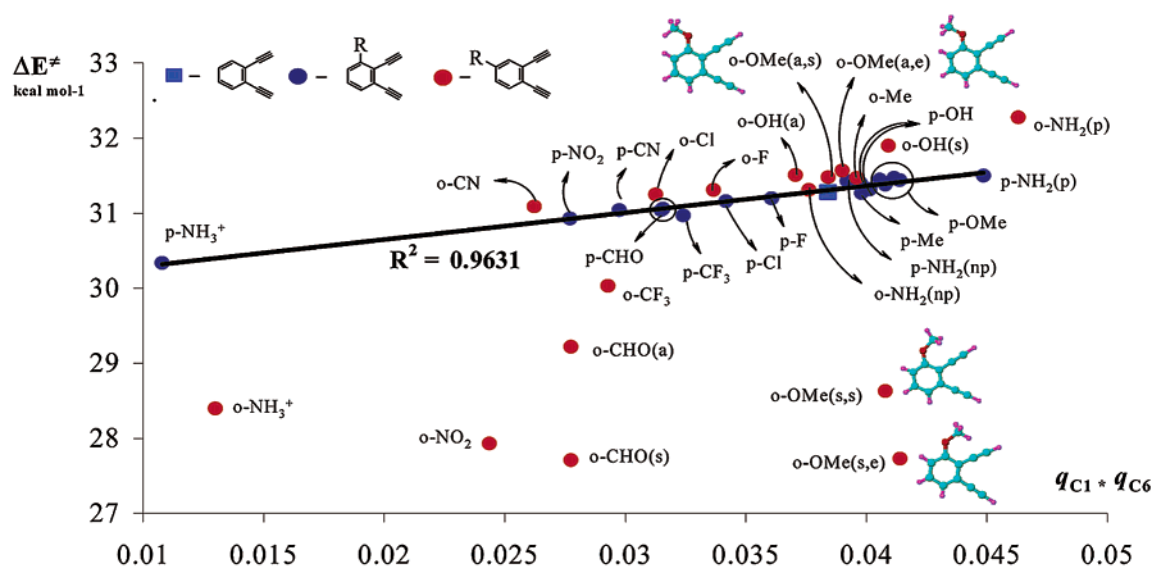


Figure 1. Correlation between the calculated activation energy of the Bergman cyclization and the product of natural charges at the terminal acetylenic atoms of benzannulated enediyne. Only para substituents obey the correlation.

substituents lie within a range of only 0.6 kcal/mol (Table 1). A larger decrease in the activation energy for a positively charged substituent (NH_3^+) demonstrates the predominant role of the field effect.

The field effect of electronegative substituents decreases electron density at the terminal acetylenic atoms thus alleviating the electron repulsion. We found that this simple rationale is supported by an excellent correlation of the

products of natural atomic charges^{18,19} at the acetylenic carbons with the activation energy (Figure 1).

However, the influence of ortho substituents on the activation energy is not limited to the field effect, as indicated by large deviations from the above correlation (Table 1 and Figure 1). As a result the accessible range of activation energies is much larger, from 27.7 to 32.3 kcal/mol. At 37 °C, all other factors being equal, it corresponds to an almost 2000-fold change in the reaction rate!¹⁸ This difference is especially remarkable since the electronic effects of ortho and para substituents are often considered similar.¹²

Further insight into the role of ortho substituents is provided from the difference in absolute energies between *ortho*- and *para*-substituted enediyne (δE_R) as well as their cyclized TSs (δE_{TS}) given in Table 1. Positive values of δE_R and δE_{TS} are indicative of steric repulsion and lower stabilities of the ortho compounds compared to those of the corresponding para compounds. Negative values of δE_R and δE_{TS} indicate that ortho isomer is more stable as a result of stabilizing interactions of the substituent with the enediyne moiety. It is important to note here that only difference between δE_R and δE_{TS} and not the sign of the δE s determines the effect of the substituent on the cyclization rate.

Sterically compact ortho substituents such as Me, OH, *anti*-OMe, F, Cl, and CN destabilize the ground and transition states to a similar degree. As a result, changes in the activation energy are minor. The net effect of these substituents on the cyclization rate is similar to that of the para substituents, and the corresponding computational data fit well into the correlation in Figure 1.

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(14) The size of the systems precluded the use of accurate but computationally expensive multiconfigurational methods. (a) Nicolaides, A.; Borden, W. T. *J. Am. Chem. Soc.* **1993**, 115, 11951. (b) Lindh, R.; Lee, T. J.; Bernhardsson, A.; Persson, B. J.; Karlström, G. *J. Am. Chem. Soc.* **1995**, 117, 7186. (c) Kraka, E.; Cremer, D.; Bucher, G.; Wandell, H.; Sander, W. *Chem. Phys. Lett.* **1997**, 268, 313. (d) McMahon, R. J.; Halter, R. J.; Fimmen, R. L.; Wilson, R. J.; Peebles, S. A.; Kuczkowski, R. L.; Stanton, J. F. *J. Am. Chem. Soc.* **2000**, 122, 939. (e) Cramer, C. J.; Nash, J. J.; Squires, R. R. *Chem. Phys. Lett.* **1997**, 277, 311. Cramer, C. J.; Squires, R. R. *J. Phys. Chem. A* **1997**, 101, 9191.

(15) UB3LYP/6-31G** slightly overestimates the reaction barrier and underestimates the endothermicity (see Supporting Information). However, this accuracy is acceptable since we are considering *relative* trends in reactivity.

(16) (a) Kraka, E.; Cremer, D. *J. Am. Chem. Soc.* **2000**, 122, 8245. (b) Gräfeint, J.; Hjerpe, A. M.; Kraka, E.; Cremer, D. *J. Phys. Chem.* **2000**, 122, 8245. (c) Jones, G. B.; Warner, P. M. *J. Am. Chem. Soc.* **2001**, 123, 2134. (d) Feldgus, S.; Shields, G. C. *Chem. Phys. Lett.* **2001**, 347, 505.

(17) BLYP is another DFT method commonly used for theoretical studies on the Bergman cyclization: Prall, M.; Wittkopp, A.; Fokin, A. A.; Schreiner, P. R. *J. Comput. Chem.* **2001**, 22, 1605. Prall, M.; Wittkopp, A.; Schreiner, P. R. *J. Phys. Chem.* **2001**, 105, 9265. (See Supporting Information.)

(18) The product of atomic charges is proportional to the electrostatic repulsion between the atoms (with constant interatomic distance).

(19) Weinhold, F.; Natural Bond Orbital Methods. In *Encyclopedia of Computational Chemistry*; Schleyer, P. v. R., Ed.; Wiley: New York, 1998; Vol. 3, p 1792.

On the other hand, the presence of *ortho*-NO₂, NH₂, NH₃⁺, CHO, CF₃, and *syn*-OMe groups results in large changes in the activation energy. Depending on the substituent, three different factors account for these changes: steric assistance²⁰ (decrease in steric destabilization in TS), extra stabilization of the TS, and decrease in TS stabilization. The first two factors decrease the activation energy.

syn-CHO, NO₂, CF₃, and *syn*-OMe facilitate the cyclization through steric assistance. The ground state is destabilized by steric factors as reflected in the decreased C₁–C₆ distances for the *ortho* isomers and higher energies of the latter (more than 5 kcal/mol for *syn*-OMe and NO₂). The steric effects are alleviated in the TS where the acetylene moiety is bent away from the *ortho* substituent.

An interesting feature of sterically demanding substituents is the dependence of the activation energy on the conformation. This conformational dependence of the Bergman cyclization may provide an additional way to control reactivity of enediynes *in vivo* when binding to the minor groove of DNA is conformer specific.

However, Curtin-Hammett analysis shows that *syn*-conformers are unlikely to contribute significantly to the rate of the Bergman cyclization of 2,3-diethynylanisole because these conformers are destabilized significantly compared with the lowest energy (a,s)-conformer (3.9 kcal mol^{−1} (s,s) and 6.5 kcal mol^{−1} (s,e)). Although the 2-fold difference in the reaction rates for cyclization of 1,2-diethynylbenzene and 2,3-diethynylanisole is consistent with the small difference (0.2 kcal mol^{−1}) in the computed barrier, theory predicts the anisole to be *less* reactive. Thus, at this stage, theory does not provide a definitive explanation for the subtle increase in the reactivity of the *ortho*-OMe enediyne. An intriguing possibility is that the diradical is trapped intramolecularly by the *ortho*-methoxy group.²¹ This trapping might prevent the retro-Bergman ring opening and make the cyclization step irreversible. We plan to seek further insight into the details of the hydrogen atom abstraction using isotope labeling and to carry out additional kinetic studies to determine the rate-limiting step in the cycloaromatization cascade.

CH₃, NH₂, and *syn*-OH increase the activation energy because they stabilize the starting material by a hydrogen bond between the X-H moiety and *in-plane* acetylenic π -orbital. The strength of the hydrogen bond increases with the electronegativity of X.²² This interaction results in an increase of the C₁–C₆ distance and outward bending of the acetylene group. As the reaction proceeds, the stabilizing

interaction disappears since the overlap of σ^*_{X-H} orbital and the in-plane π -bond decreases as a result of inward bending of the acetylene moiety away from the X–H group.

In contrast, in the case of a positively charged functional group, NH₃⁺, the strength of hydrogen bonding *increases* at the beginning of the cyclization step, thus providing extra stabilization to the TS. This accelerating effect can be attributed to a larger electrostatic component in the H-bonding in the case of a positively charged group and to a concomitant strong through-space electron transfer from the adjacent *in-plane* π -bond of acetylene moiety to the ammonium group. As a result, population of this π bond is markedly decreased (Table 3, Supporting Information), thus decreasing electron repulsion in the transition state.

The large decrease in the activation energy upon protonation is important because cancer cells are more acidic (pH 5.5²³) than normal cells. At this pH, anilines are protonated noticeably.²⁴ Hence, the fact that protonation of the *ortho*-amino group decreases the activation energy by 3.9 kcal/mol (and thus can speed up the reaction by the factor of 600 at 37 °C) can be used in the design of tumor-specific DNA cleaving agents.^{16, 25}

In conclusion, we have found that the Bergman cyclization of aromatic enediynes is highly sensitive to *ortho* substitution as a result of a combination of electronic, steric, and electrostatic effects. This finding opens possibilities for the rational design of and conformer-specific and pH-dependent DNA-cleaving agents.

Acknowledgment. A.I. thanks Florida State University for First Year Assistant Professor Award and Ms. Carol Joud for technical assistance.

Supporting Information Available: Optimized geometries and energies for all compounds, synthetic procedures, and spectral and kinetic data for 2,3-diethynylanisole and 1,2-diethynylbenzene. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(20) Eliel, E. L.; Wilen, S. H.; Doyle, M. P. *Basic Organic Stereochemistry*; Wiley-Interscience: New York, 2001; p 459.

(21) The activation barrier for the intramolecular hydrogen abstraction is 6.7 kcal/mol, and the reaction is 9.2 kcal/mol exothermic (UB3LYP/6-31G**).

(22) NBO analysis¹⁸ finds the following energies for the hydrogen bonds (in kcal/mol). 1.3 (NH₂), 2.7 (*syn*-OH), 5.2 (NH₃⁺). Interestingly, direct orbital interaction of substituents at the vinylic position with the developing radical center can be either stabilizing or destabilizing.^{16c}

(23) Osinsky, S.; Bubnovskaya, L. *Arch. Geschwulstforsch.* **1984**, *54*, 463. Tannock, I. F.; Rotin, D. *Cancer Res.* **1989**, *49*, 4373.

(24) Basicity of *ortho*-amino-enediynes is unknown, but it is reasonable to suggest that the protonation will occur to a noticeable extent and can be further controlled by substitution. Aniline (pK_b = 9.40) is 7% protonated and *p*-anisidine (pK_b = 8.70) is 29% protonated at pH 5.5.

(25) Hoffner, J.; Schottelius, J.; Feichtinger, D.; Chen, P. *J. Am. Chem. Soc.* **1998**, *120*, 376–385.