

Cyclic enediyne: relationship between ring size, alkyne carbon distance, and cyclization barrier

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This work presents the first detailed study on a series of cyclic hydrocarbon enediyne showing that the cyclization barrier depends upon the ground state energy differences of the biradical products, and that pure density functional methods can be used reliably to estimate the activation enthalpies of the Bergman reaction.

While the Bergman-3-ene cyclization¹ of (*Z*)-hex-1,5-diyne (**1**, enediyne) is driven thermodynamically by subsequent formation of two C–H bonds, the pharmacological activity² of cyclic enediyne (**3**)³ is also related to changes in ring strain upon cyclization.^{4,5} Ring closure in enediyne carrying drugs complexed to the minor groove of DNA is triggered by subtle structural perturbations.⁴ Hence, enediyne are highly promising pharmacophors, but reactivity control is still a problem.

It has been suggested that if the distance *d* of the acetylene carbons forming the new bond is in the critical range of 3.31–3.20 Å, cyclization should occur at room temperature.⁶ Based on experimental activation enthalpies, X-ray structures of C₉–C₁₂ cyclic enediyne and empirical computations, it was proposed that differential molecular strain in the educts and transition states is most important.^{7–10} There have been several studies attempting to clarify the relationship between *d* and cyclic enediyne cyclization as well as the ground state energy differences, but transition structures for other than the smallest enediyne were never computed.^{9–14} The modeling of larger enediyne is currently only possible with molecular mechanics,¹³ semiempirical^{10,14} or lowest-level *ab initio* methods,¹¹ but these cannot be used to compute accurate enediyne transition structures and activation energies; much higher level treatments are needed.^{12,15,16} Density functional theory (DFT) offers a suitable compromise for multi-reference cases, as it is the electron density instead of the wavefunction which is the decisive quantity.¹⁷ While hybrid Hartree-Fock DFT methods like B3LYP do not perform well for computing the heat of

formation of *p*-benzyne **2a**,¹⁶ ‘pure’ (*i.e.* non-hybrid DFT treatments give acceptable accuracy (Table 1).¹⁸ We have therefore used the BLYP/6-311+G**//BLYP/6-31G* level throughout, unless noted otherwise.¹⁹

The experimental activation enthalpies are well reproduced at our reference level: (theory vs. expt.) 28.4 vs. 28.2 kcal mol⁻¹ for **TS1a**;²⁰ 25.0 vs. 23.8⁶ and 24.0 kcal mol⁻¹ for **TS3d**.²¹ Enediyne **1a** and **1b** have almost the same *d* value but the difference in ΔH^\ddagger values is 7 kcal mol⁻¹. This is primarily due to the fact that methyl groups stabilize (by *ca.* 10 kcal mol⁻¹) acetylenic (**1b**) much more than olefinic bonds (partially developed in **TS1b**). Thus, dialkyl substitution increases both the activation barriers and the reaction endothermicities of the Bergman reaction for acyclic enediyne.

As expected, both **3a** and **3b** do not cyclize, despite small *d* values; **5** was found experimentally not to cyclize either.²² The cyclization products would contain highly strained [olefin strain (OS) = 54.4 kcal mol⁻¹, Table 1]²³ cyclopropene (in **3a**) and cyclobutene moieties (in **3b** and **5**; OS = 30.6 kcal mol⁻¹).²³ Nine-membered **3c** was suggested to cyclize spontaneously at room temperature,^{4,6} and the relatively low activation barrier of 16.3 kcal mol⁻¹ for **TS3c** supports this finding. While **3d** with *d* = 3.413 Å²¹ cyclizes spontaneously at room temp., **3e** does not, despite *d* being only slightly larger (3.588 Å).⁴ Part of the activation enthalpy difference (7 kcal mol⁻¹) is due to olefin strain (OS) energy differences²³ between the cyclohexene (OS = 2.5 kcal mol⁻¹) and cycloheptene (OS = 6.7 kcal mol⁻¹) moieties in the products. Thus, there is no linear relationship between the alkyne carbon distance *d* and ΔH^\ddagger for Bergman-cyclization of monocyclic enediyne.

The reaction enthalpy ($\Delta_r H_{OK}$, Table 1) of the Bergman reaction is more difficult to compute than the activation enthalpies due to the pronounced multi-reference-character of

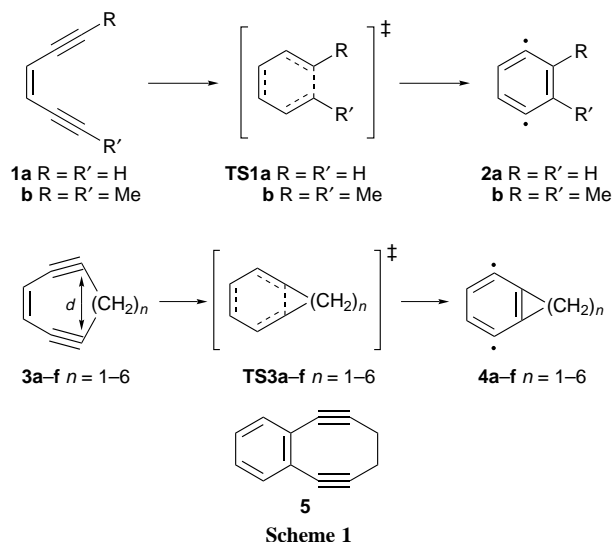


Table 1 Parameter *d* (in Å), activation enthalpy (ΔH^\ddagger /kcal mol⁻¹), reaction enthalpy ($\Delta_r H_{OK}$ /kcal mol⁻¹) for the Bergman reaction of **3a–f**; olefin ring strain (OS) of non-benzenoid product ring and stability of enediyne at room temperature. Level of theory: BLYP/6-311+G**//BLYP/6-31G*, unless noted otherwise

Ring size	Species (PG) ^a	<i>d</i>	ΔH^\ddagger	$\Delta_r H_{OK}$	Corrected ^b $\Delta_{cr} H_{OK}$	OS ^c	Stable at 25 °C
—	1a (C _{2v})	4.548	28.4	17.6	8.5	—	yes ^d
—	1b (C _{2v})	4.571	35.6	29.9	20.8	—	yes ^d
7	3a (C _{2v})	2.512	— ^e	—	—	54.4	n.a.
8	3b (C _{2v})	2.636	— ^e	—	—	30.6	yes ^f
9	3c (C _s)	2.924	16.3	11.4	2.3	6.8	no ^g
10	3d (C ₂)	3.413 ^h	25.0 ⁱ	18.3	9.2	2.5	no ^g
11	3e (C ₂)	3.588 ^j	31.9	25.4	16.3	6.7	yes ^g
12	3f (C ₂) ^k	4.353	40.3	36.3	27.2	7.4	yes ^g

^a PG = point group. ^b Corrected for the computational error in $\Delta_r H_{OK}$ of **2a** at 0 K (correction = -9.1 kcal mol⁻¹). ^c Ref. 23. ^d Ref. 24. ^e No ring closure, see text. ^f Ref. 22. ^g Ref. 6. ^h Experimentally estimated distance *ca.* 3.4 Å (refs. 24 and 21). ⁱ Experimental activation barrier = 23.8 (ref. 6) and 24.0 kcal mol⁻¹ (refs. 14 and 21). ^j Experimental distance (X-ray) = 3.661(5) Å (ref. 6). ^k Using a 6-311G** basis set for the energy single point. Despite extensive efforts, the wavefunction did not converge with added diffuse (+) functions on the heavy atoms.

2a. It is therefore sensible to correct $\Delta_r H_{\text{OK}}$ for the error (9.1 kcal mol⁻¹) in evaluating the enthalpy of the parent reaction. This correction seems reasonable based on the fact that nine- and ten-membered enediynes cyclize reversibly.^{4,24} Larger enediyne cyclizations are much more endothermic and the corresponding transition structures are product-like.^{12,15} This is confirmed by the increase in the activation enthalpy of the parent (**1a** → **TS1a**; $\Delta H^\ddagger = 28.4$ kcal mol⁻¹) vs. the dimethyl enediyne system (**1b** → **TS1b**; $\Delta H^\ddagger = 35.6$ kcal mol⁻¹): **TS1b** already experiences part of the higher relative energy of the product, where the methyl groups at olefinic carbons are less stabilizing.

The relationship between ΔH^\ddagger for Bergman cyclization of monocyclic enediynes can thus roughly be estimated from the endothermicity of eqn. (1).

$$\Delta H^\ddagger = \Delta_{\text{cr}} H_{\text{OK}} + 14 \pm 2 \text{ kcal mol}^{-1} \quad (1)$$

In conclusion, there is excellent agreement between the experimental and pure DFT-computed ΔH^\ddagger values for Bergman cyclization of monocyclic enediynes. There is no predictive linear relationship between d and ΔH^\ddagger , but the 'critical range' for 3.31–3.2 Å for spontaneous cyclization may be extended to 3.4–2.9 Å. However, cyclization may be inhibited by large olefin strain in the products. Although dialkyl substitution increases the endothermicity of the Bergman reaction, ring strain effects can dominate.

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Notes and References

* E-mail: pschrei@gwdg.de Coordinates of all optimized structures are available through the author by e-mail request.

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