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Benzannelation Alters the Rate Limiting Step in Enediyne Cycloaromatization

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Abstract: The rate-limiting step in the Bergman reaction was changed from cyclization to hydrogen-abstraction by benzannelation. This effect should be attributed to the faster rate of the retro-Bergman cyclization and/or the slower rate of hydrogen abstraction by the aromatic ring condensed 1,4-didehydrobenzene intermediate.

Keyword: Bergman reactions; Radicals and radical reactions; Steric and strain effects; Aromaticity

Bergman and co-workers established that the cyclization step is rate-determining in the cycloaromatization reaction of aliphatic enediynes[1,2]. However, we recently found that the cycloaromatization rates of nine-membered cyclic enediynes **1** and the C-1027 chromophore are dependent upon the presence of solvents which act as hydrogen donors[3]. This event indicated that the hydrogen abstraction caused by *p*-benzyne-type biradical intermediate **2** is kinetically significant, suggesting that the rate of hydrogen abstraction is about 100 times slower than that of the phenyl radical. Chen and co-workers showed that the reactivity of 9,10-dehydroanthracene is similarly lowered[4]. On the other hand, the reaction rate of ten-membered cyclic enediyne **4** that yields 1,2,3,4-tetrahydroanthracene is dependent upon the concentration of 1,4-cyclohexadiene[5]. The kinetic behavior of **4** and **1** differs from that shown by Bergman[1]. The high strain in **1** and **2** due to the nine-membered enediyne and the epoxypentalene structure, respectively, destabilize **1** and **2** substantially and therefore lower the activation barriers between **1** and **2** so that kinetically significant hydrogen abstraction and the equilibration between **1** and **2**, even at ambient temperature, are established as previously described[3a]. In this communication, we investigated the mechanistic reason for the reactivity of **4**. A conceivable explanation for the disparity would be a ring strain effect because **4** and **1** are strained ten- and nine-membered cyclic enediynes with a strain energy of 10 and 14 kcal/mol, respectively, according to the MM2 calculation[6], in contrast to the acyclic systems studied by Bergman[1]. We now disclose that ring strain is not responsible, whereas benzannelation is crucial.

To clarify the role of ring strain, we initially examined the effect of radical trapping agents on the decay rate of a ten-membered enediyne **7** with no benzene ring. The activation energy for the cycloaromatization of **7** to give 1,2,3,4-tetrahydronaphthalene has been reported, yet the trapping agent effect has not been described[7]. The concentration of 1,4-cyclohexadiene in benzene-d_6 was changed as shown in Table 1. The kinetic data indicate that the decay of **7** is independent of the concentration of trapping agent. Consequently the cyclization

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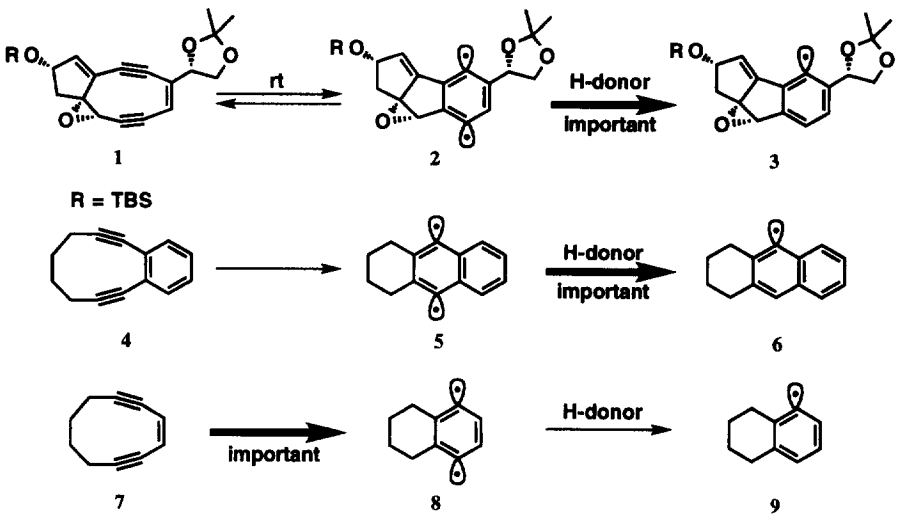


Figure 1. Kinetically important step in cycloaromatization of strained cyclic enediynes

Table 1
Effect of 1,4-cyclohexadiene concentration on the disappearance rate of **7** (10 mM) in benzene-d_6 at 57 °C[a]

Conc. of 1,4-CHD[b] / M	k / 10^{-4} s^{-1}	$t_{1/2}$ / h
0.10	1.19	1.61
0.25	1.13	1.71
0.50	1.10	1.75
1.32	1.14	1.69
2.48	1.14	1.69
5.29	1.13	1.71
10.50 (neat)	1.12	1.72

[a] Measured by HPLC.
[b] 1,4-Cyclohexadiene.

Table 2
Effect of 1,4-cyclohexadiene concentration on the disappearance rate of **4** (10 mM) in benzene-d_6 at 89 °C[a]

Conc. of 1,4-CHD[b] / M	k / 10^{-6} s^{-1}	$t_{1/2}$ / h
0.10	3.88	49.6
0.25	7.65	25.2
0.50	13.7	14.1
1.32	28.2	6.83
2.48	37.6	5.13
5.29	48.2	4.00
10.50 (neat)	46.0	4.19

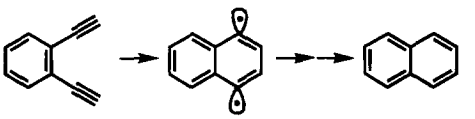
[a] Measured by HPLC.
[b] 1,4-Cyclohexadiene.

step of **7** should be rate-determining as expected (Figure 1).

We re-examined the decay of **4**, which has been reported to depend upon the concentration of 1,4-cyclohexadiene[5]. Table 2 shows the dependence of the rate on the trapping agent. The hydrogen abstraction step in the Bergman reaction of **4** is kinetically significant in contrast to that of **7** (Figure 1). Therefore, ring strain is not responsible for the alteration of the kinetically significant step, but the benzannelation appears to be crucial. Cycloaromatization of 2,3-diethynylbenzene (**10**) which yields naphthalene (**12**)[8] was then examined, since **10** is a simple analogue of acyclic (Z)-hex-3-ene-1,5-diyne which did not show a hydrogen donor effect on the cycloaromatization[1]. The disappearance rate of **10** at 152℃ was affected by the

concentration of 1,4-cyclohexadiene as shown in Table 3. Furthermore, 2,3-diethynylnaphthalene (**13**) also exhibited a hydrogen donor-dependent decay at higher concentrations of 1,4-cyclohexadiene (Table 4); at lower (<1.0 M) concentrations of the hydrogen donor, only polymeric products were formed. Thus, benzannelation is the crucial factor for altering the rate-determining step.

Table 3
Effect of 1,4-cyclohexadiene concentration on the disappearance rate of **10** (10 mM) in benzene-d_6 at 152 °C[a]



10 **11** **12**

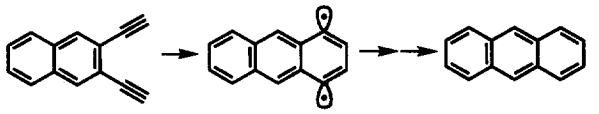
Conc. of 1,4-CHD[b] / M	k / 10^{-5} s^{-1}	$t_{1/2}$ / h
0.10	4.70	4.10
0.25	8.52	2.26
0.50	9.56	2.01
1.50	11.7	1.65
2.50	12.8	1.51
5.29	17.3	1.11
10.50 (neat)	15.7	1.23

[a] Measured by GC.
[b] 1,4-Cyclohexadiene.

This benzannelation effect should be attributable to the change of the relative rate between the retro-Bergman cyclization from the biradical intermediate and the corresponding hydrogen abstraction step. A simple interpretation is that the rate from **5** to **4** becomes faster than that from **5** to **6** because only part of the resonance energy of **5** is lost in the reversion process in comparison with the full loss of aromaticity of **8**[9]. Another possibility is that the hydrogen abstraction by **5** might be retarded compared to **8**. Calculations[10] and a recent experiment[11] indicated that a *p*-benzyne singlet state is only a few kcal/mol more stable than the triplet due to through-bond coupling. Based on Chen's rationale that the *p*-benzyne biradical in a low-lying singlet is a poor hydrogen abstraction agent[4b], we assume that benzannelation induces a substantial singlet-triplet splitting. Thus, the aromatic ring annelated biradical **5** would have a lower reactivity than biradical **8** because of the larger singlet-triplet gap.

In conclusion, benzannelation alters the rate limiting step in enediyne cycloaromatization. This effect should be attributable to the faster rate of the retro-Bergman cyclization from the aromatic ring condensed 1,4-didehydrobenzene biradicals and/or the slower rate of hydrogen abstraction by them. The possibility of the latter hypothesis is under investigation in our laboratory.

Table 4
Effect of 1,4-cyclohexadiene concentration on the disappearance rate of **13** (10 mM) in benzene at 152 °C[a]



13 **14** **15**

conc. of 1,4-CHD[b] / M	k / 10^{-5} s^{-1}	$t_{1/2}$ / h	Yield of **15** / %
1.76	4.02	4.80	37
2.64	6.37	3.02	18
5.29	7.63	2.52	51
10.50 (neat)	7.53	2.56	65

[a] Measured by GC.
[b] 1,4-Cyclohexadiene.

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