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Remarkable Kinetic Solvent Isotope Effect on the Cycloaromatization of C-1027 Chromophore, a 9-Membered Enediyne, and the Thermochemistry

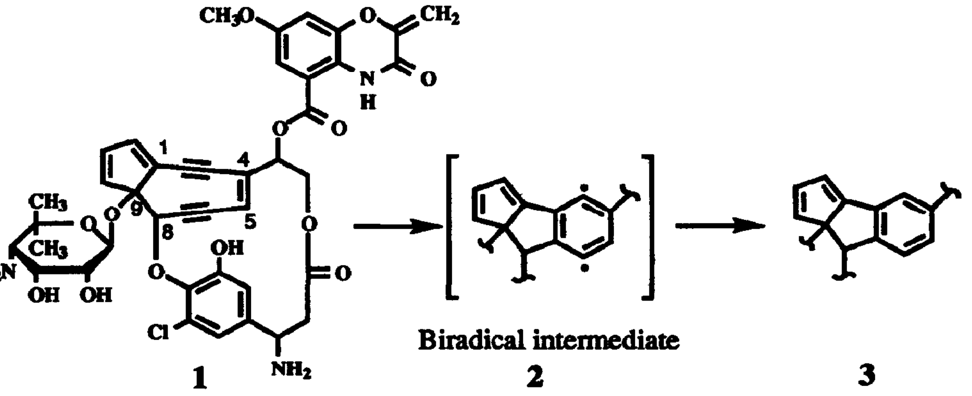
Ken-ichiro Yoshida,* Yoshinori Minami and Toshio Otani
Tokushima Research Center, Taiho Pharmaceutical Co., Ltd.
Kawauchi-cho, Tokushima 771-01, Japan

Yukio Tada
Hanno Research Center, Taiho Pharmaceutical Co., Ltd.,
Misugidai, Hanno, Saitama 357, Japan

Masahiro Hirama
Department of Chemistry, Faculty of Science, Tohoku University,
Sendai 980-77, Japan

Abstract: Remarkable kinetic solvent isotope effect, experimental activation energy (15.1 kcal/mol) as well as MO calculations present a reaction energy diagram for cycloaromatization reaction of C-1027 chromophore, a highly strained 1,5-diyn-3-ene molecule.

Recently, the chromophores of C-1027[1] and kedarcidin,[2] active principles of extremely potent anti-tumor antibiotics, have been disclosed to possess a highly strained 9-membered 1,5-diyn-3-ene structure. The biological activities of these enediynes could be attributed to the DNA double-strand scission by phenylene 1,4-diyl radical intermediate formed through Masamune-Bergman cycloaromatization reaction.[3] Another 9-membered enediyne, neocarzinostatin chromophore is known to generate indene biradical species through Myers-type rearrangement, and the chemistry and the kinetics were investigated.[4] However, the thermochemical kinetics of the cycloaromatization of natural[1,2] and synthetic[5] 9-membered 1,5-diyn-3-ene systems have not been defined well due to their extreme instabilities.[6] In this communication, we disclose the kinetics of the cycloaromatization of C-1027 chromophore (C-1027-Chr) **1** and its energetics.



Scheme 1. The cycloaromatization of C-1027-Chr (1).

Decomposition rates of **1** in various solvents were monitored by HPLC (Table 1). The cycloaromatization product **3** was detected only in the reactions in alcoholic or ethereal solvents, such as dioxane, THF, MeOH and EtOH. The highest yield of 3 was obtained in EtOH. Interestingly, unprecedented remarkable kinetic isotope effects were observed when deuterated solvents were used as shown in Table 2. These results show that the rate of the transformation of 1 to 3 was affected by the hydrogen abstraction step in contrast to the acyclic enediyne systems in which the cyclization leading to the biradical is rate-limiting.[7,8]

Table 1. Degradation of C-1027-Chr (1) in various solvents.

Solvent[a)]	k (s^{-1})[b)]	t1/2 (hr)	Yield of 3 (%)
EtOH	2.46 x 10-4	0.8	82
MeOH	2.06 x 10-4	1.0	0[d)]
dioxane	1.15 x 10-4	1.6	50
THF	> 1.5 x 10-3	< 0.1	39[d)]
$CHCl_3$	3.44 x 10-4	0.5	0
EtOAc	6.16 x 10-5	3.0	0
CH_3CN	5.65 x 10-5	2.8	0
DMSO	6.17 x 10-5	3.1	0
DMF	> 1.5 x 10-3	< 0.1	0
BRB[c)] (pH 3)	1.82×10^{-5}	10.6	0

a) Concentration of 1 lower than 10 nM at room temperature (~25°C).
b) The correlation coefficients were within the limit of 0.94~0.9997.
c) Britton-Robinson buffer (0.04M CH_3COOH, H_3PO_4, H_3BO_3 / 0.2N NaOH)
d) The aromatization product (3) was further degraded by methanolysis or hydrolysis.

Table 2. Kinetic isotope effects on the cycloaromatization of 1 at 50°C.

Solvent	k (s^{-1})[a)]	t1/2 (hr)	Yield of 3 (%)	k_H/k_D
dioxane	9.25×10^{-4}	0.15	52	
dioxane-d_8	3.14×10^{-4}	0.59	18	2.9
CH_3OH[b)]	3.49×10^{-4}	0.56	46	
CH_3OD[b)]	3.33×10^{-4}	0.54	58	1.1
CD_3OD[b)]	1.27×10^{-4}	1.50	13	2.8
C_2H_5OH	1.75×10^{-3}	0.12	85	
C_2D_5OD	4.57×10^{-4}	0.44	58	3.8

a) The correlation coefficients were within the limit of 0.996~0.9999.
b) The solution pH or pD was adjusted to 3 with H_3PO_4 to prevent the methanolysis of 3.

In order to understand this unprecedented kinetic isotope effect and to establish the energy diagram, we first measured the reaction rate of the cycloaromatization of 1 in EtOH at 40, 50, and 60°C and obtained the activation energy of 15.1 kcal/mol (lnA = 17.0, r = 0.995). Under these conditions, 3 was formed in 85~90% yield. The semi-empirical PM3[9] calculations of several enediyne systems were then performed to estimate the relative potential energies of 1 and biradical intermediate 2 (Fig. 1). The calculation represented well the difference of their heats of formation for (Z)-hex-3-ene-1,5-diyne 4 and p-benzyne 5, while their absolute values are about 10 kcal/mol smaller than their reconciled ones, respectively.[10] The decrease of the calculated endothermicity for 10-membered 6 and 9-membered 8 are reasonable, since the ground states of these cyclic enediyne systems are expected to be destabilized by the ring strain. The simple cyclonon-3-en-1,5-diyne system 8 is presumed to be almost isothermal with 9 due to the extreme ring strain. However, the core system

10 of C-1027-Chr were predicted to be as endothermic as the acyclic system **4**. This would arise from the destabilization of **11** due to the strain of dihydropentalene structure,[11] together with the stabilization of **10** due to the extended conjugation of enediyne system. Thus, the potential energy of **2** relative to **1** was roughly estimated to be ~12.5 kcal/mol. The energy barrier for the cycloreversion of **2** to **1** is anticipated to be as small as ~2.6 kcal/mol. Therefore, the first step, cyclization of **1** leading to the biradical **2**, should be reversible at room temperature, but **2** with high potential energy can not be detected by spectroscopic techniques. The energy barriers for the second step, hydrogen abstraction reactions, would be approximately equal to that of the aliphatic hydrogen abstraction by phenyl radical, ~7 kcal/mol,[12] which is a little larger than the barrier for the cycloreversion of **2** to **1**.

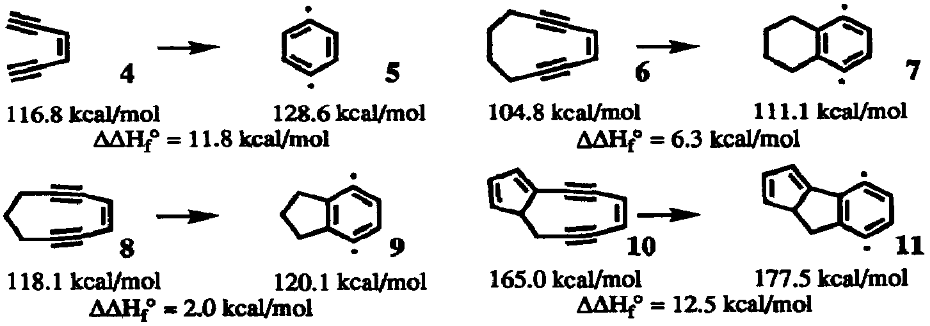
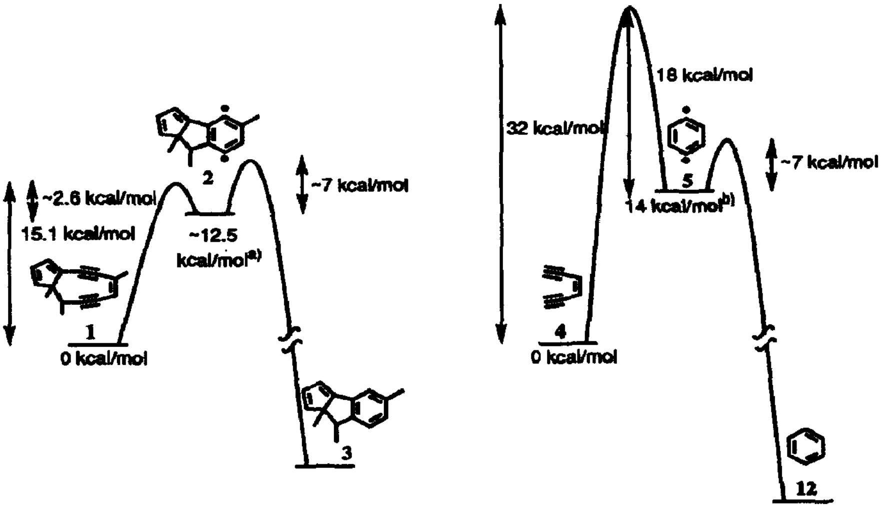


Fig. 1 Heats of formation calculated by PM3.



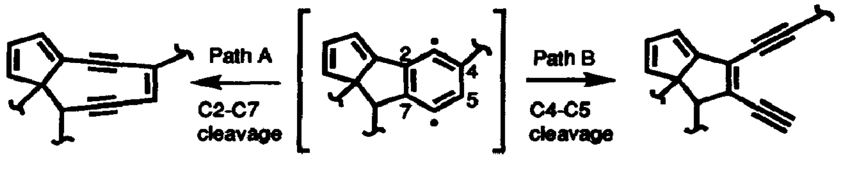
a) Estimated by PM3 calculation in this study.

b) Estimated by revised group additivities for 4[4] and heat of formation for 5.[10]

Fig. 2 Energy diagram for the cycloaromatization reaction of C-1027-Chr (1) and acyclic enediyne (4).

Consequently, the energy diagram for the cycloaromatization of **1** is postulated as shown in Fig.2. The most striking difference between the cycloaromatizations of **1** and **4** is the energy barriers between enediyne and biradical. The high barrier between **4** and **5** render the biradical generation to be rate-limiting. By contrast, the low barrier from **1** to **2** and more facile cycloreversion of **2** to **1** results in the dependency of the reaction cascade rate on the hydrogen atom abstraction process around the room temperature.

If the biradical generation from **1** is reversible as discussed above, one question arises: why **2** does not go back to **13** ? Two pathways A and B are possible for the retro-Bergman reaction of **2** as shown in Scheme 2. As expected from Fig. 2, path B to the acyclic enediyne system needs a larger barrier relative to path A. In addition, PM3 calculation of **11** indicates the bond order of C2-C7 is smaller (1.21) and its bond length is longer (1.44 Å) than those of C4-C5 (1.35 and 1.41 Å respectively). These data suggest that the C2-C7 bond should be much easier to be cleaved than the C4-C5 bond.



1 **2** **13**

Scheme 2 Possible reaction pathways for retro-Bergman reaction of biradical (3).

The thermochemistry of **1** discussed above, is in agreement with the recent observation reported by Sugiura et al.[13)] that the life time of **1** in the presence of DNA is shorter than that without DNA in the aqueous medium, since DNA is likely to be a good hydrogen atom donor.

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