Tautomer-Dependent Bergman Cyclization of Novel Uracil – Enediyne Chimeras

Chang-Sik Kim, Christian Diez, and Keith C. Russell*[a]

Abstract: Uracil – enediyne chimeras **4**, **7**, and **8** were prepared and examined for their propensity to undergo Bergman cyclization. Kinetic experiments showed lactam tautomers **7** and **8** reacted up to 25 times faster than lactim ether **4**. Determination of the activation energy for each cycloaromatization reaction, along with radical trapping agent dependent studies, indicate the rate differences result from different ground state energies of the starting enediynes.

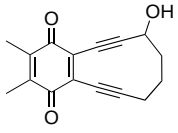
Keywords: cyclizations · diradicals · electrocyclic reactions · enynes · tautomerism

Introduction

The Bergman cyclization is generally considered as the thermally allowed electronic rearrangement of a (*Z*)-3-ene-1,5-diyne to a *p*-benzyne diradical.[1] This diradical is subsequently quenched to afford a new benzene ring. While first observed in the late 1960s and more completely analyzed in the early 1970s, this reaction underwent a renaissance in the mid-1980s with the structural elucidation of a series of naturally occurring antibiotics whose cytotoxic activity was associated with a Bergman cyclization.[2]

Enormous effort has been put forth in developing methods to activate the Bergman cyclization for both synthetic and biological applications. Most enediynes are activated by contraction of the distance between the triple bond termini. Synthetic models have utilized acidity,[3] basicity,[4] photochemistry,[5] and metal coordination[6] to ultimately bring the ends of the triple bonds close enough to react. Enediynes have also been converted to more reactive eneynallenes by nucleophilic addition,[7] elimination,[8] sigmatropic rearrangement,[9] and organometallic[10] means, again resulting in molecules with large strain energies.

Compared to the use of steric strain, relatively little effort has been invested in examining the detailed electronic contributions to cyclization. Schmittel and Kiau demonstrated that electron-withdrawing groups attached to the triple bond termini modestly lowered the activation enthalpy of cycloaromatization. Although not proven, it was suggested that this was the result of decreased steric repulsion between the cyclizing in-plane π orbitals.[11] Maier and Greiner hypothesized that an electron-donating arene attached to the double bond inhibited cyclization by stabilizing the ground state of the starting material more than destabilizing the transition state.[12] In a series of quinone/dihydroquinone enediyne pairs the quinone was found to react significantly faster than the dihydroquinone analogue.[13, 14] For example, quinone **1** cyclized with a half-life of 2.6 h at 110 °C, while dihydroquinone **2** cyclized with a half-life of 74 h at the same temperature. We have also reported that electron-deficient heteroarenediynes, such as **3** and **4**, have lower activation energies compared to 1,2-diethynyl benzene.[15] In addition, photochemical methods have recently been successfully employed to activate cyclization.[16]



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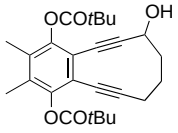

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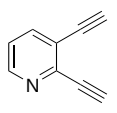

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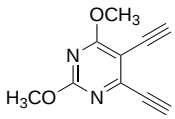

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Recently, we have been considering novel electronic methods to activate Bergman cyclization that may have useful prodrug applications. We theorized that the tautomerism found between pyrimidines and pyrimidones might act as a switch to activate Bergman cyclization as suggested in Scheme 1. The lactam and lactim tautomeric forms can be considered analogous to an electron-deficient quinone and an aromatic dihydroquinone, respectively. Therefore, it was anticipated that a lactam tautomer would undergo cyclization

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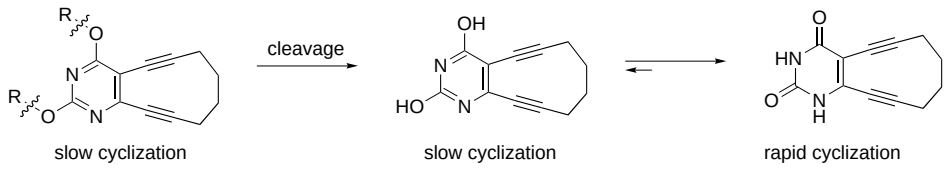


Scheme 1. Possible enediyne activation by tautomerism.

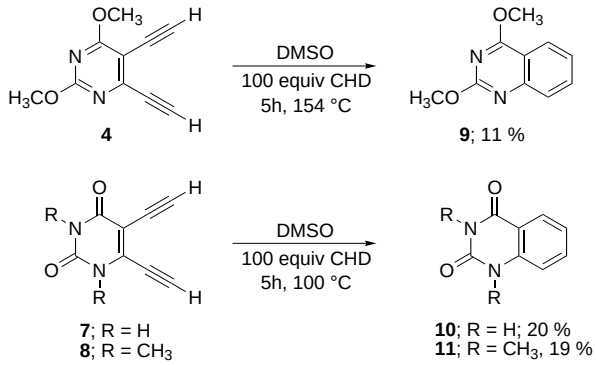
more rapidly than a lactim tautomer. This would allow cleavage of a suitable protecting group from a lactim ether to liberate a compound which could quickly equilibrate to the more reactive tautomer.

Herein we demonstrate the first tautomer-dependent Bergman cyclization. This work represents a unique example where the electronics associated with the tautomeric state of a molecule is directly associated with the rate of a chemical reaction. Furthermore, we report the first synthesis of a bis-alkynyl nucleoside base (**7**). Enediyne derivatives such as **7**, will likely be of enormous importance since they can be incorporated into oligonulceotides or peptide nucleic acids, which may serve as selective DNA or RNA cleavage agents. In addition, alkynyl uridines have received increasing interest because of their anti-AIDS and anti-herpes activities.[17]

Results and Discussion

Synthesis: Emboldened by our pervious work on heterocyclic enediyne chimera,[18] we decided to begin an investigation into the role of tautomerism on the Bergman cyclization of the pyrimidine/pyrimidone enediyne tautomers of **7**. To quantify the differential reactivity of the lactim and lactam tautomeric states of **7**, without the possibility of equilibration, *O*-methyl lactim **4** and *N*-methyl lactam **8** were prepared. The syntheses are shown in Scheme 2. Compounds **4** and **5** were prepared as previously reported.[15] Pyrimidine **5** was converted to TMS-protected uracil **6** by trimethylsilyl iodide (TMSI) mediated hydrolysis in dichloromethane in 63% yield. The reaction was slow and required careful, low-temperature (−78 °C) addition of the TMSI to avoid significant side reactions involving the triple bonds. The TMS group was then readily cleaved to afford equilibratable **7** (93%) which was alkylated to yield **8** (83%).

Cyclization: Enediynes **4**, **7**, and **8** were examined for their ability to undergo Bergman cyclization to yield **9**–**11**, respectively (Scheme 3).[19] The results are included in Table 1. All three derivatives were shown to undergo Bergman cyclization in DMSO containing 100 equivalents of 1,4-cyclohexadiene (CHD). DMSO was chosen for the cyclization studies of **4**, **7**, and **8** since it was one of a small number of solvents in which all the compounds were soluble, and hence, the results could be directly compared. The yields for the lactam tautomers were about twice that for the lactim tautomer. This is approximately the same as previously reported for a pair of lumazine–enediyne tautomer analogues.[18] The yield of **11** was time dependent. When the reaction was stopped after one hour, 40% of the starting material was recovered, along with 33% of **11**. After 5 h, with no starting material remaining, only 19% of the desired product was obtained. The remainder of the mass balance was accounted for in small amounts of DMSO adducts and intractable solids. In general, cyclizations all gave good mass balance.

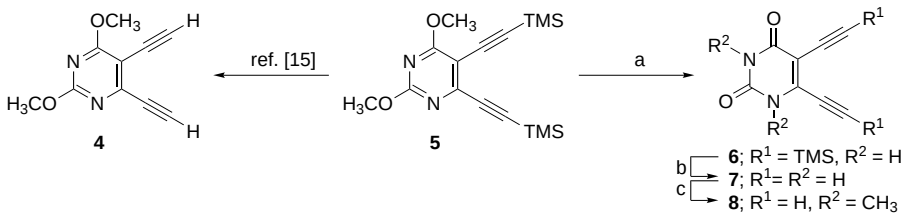


Scheme 3. Cycloaromatization of **4**, **7**, and **8**.

Table 1. Cyclization rates (k_{obs}), half-lives ($\tau_{1/2}$), and yields for **4**, **7**, and **8**.

Compd	Temp [°C]	k_{obs} [s^{-1}]	$\tau_{1/2}$ [min]	R	Yield [%][d]	Time [h]
4[a]	120	1.0×10^{-4}	115.5	0.966		
	139	2.8×10^{-4}	41.3	0.998		
	154	5.7×10^{-4}	20.3	0.998	11[e]	5
	173	1.2×10^{-3}	9.6	0.998		
7[b]	80	1.3×10^{-4}	88.9	0.996		
	100	5.7×10^{-4}	20.3	0.997	20[e]	5
	120	2.5×10^{-3}	4.6	0.995		
8[c]	84	6.0×10^{-5}	192.5	0.996		
	100	2.0×10^{-4}	57.8	0.997	33[f]	1
	120	6.6×10^{-4}	17.5	0.995	19[e]	5

[a] $E_a = 17.4$ kcal mol^{-1}, $\ln A = 13.09$ ($R = 0.993$). [b] $E_a = 20.4$ kcal mol^{-1}, $\ln A = 20.14$ ($R = 0.999$). [c] $E_a = 18.2$ kcal mol^{-1}, $\ln A = 16.004$ ($R = 0.999$). [d] Yields of isolated products from the bulk cyclization under kinetic conditions. [e] No remaining starting material. [f] 40% starting material recovered.



Scheme 2. Synthesis of **4**, **7**, and **8**. a) TMSI, CH_2Cl_2, −78 °C to room temperature, 3d (63%); b) K_2CO_3, CH_3OH, 2h, room temperature (93%); c) K_2CO_3, CH_3I, DMF, 3 h at 0°C, 12 h at room temperature (70%).

Kinetics: With confirmation of the ability of these molecules to undergo Bergman cyclization, the kinetics were examined and

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activation energies determined. Table 1 shows a summary of the results. Very quickly during our experiments it was realized that the two tautomers were markedly different. Lactam tautomers **7** and **8** were found to cyclize at reasonable rates even at 80 °C ($\tau_{1/2} = 89.9$ min and 192.5 min, respectively). The half-life of the lactim tautomer **4**, on the other hand, was more than a day at the same temperature and therefore was not accurately determined. The half-lives for **4**, **7**, and **8** were 115.5, 4.6, and 17.5 min, respectively, at 120 °C. This is a 25-fold rate enhancement for **7** over **4**. This clearly supports the notion that lactam tautomers are more reactive than lactim tautomers.

To understand the origin of the increased reactivity of the lactam compounds, the activation energies for **4**, **7**, and **8** were determined. The Arrhenius plots are shown in Figure 1. They yield activation energies of 17.4, 20.4, and 18.2 kcal mol^{-1} for **4**, **7**, and **8**, respectively. The roughly parallel lines indicate that

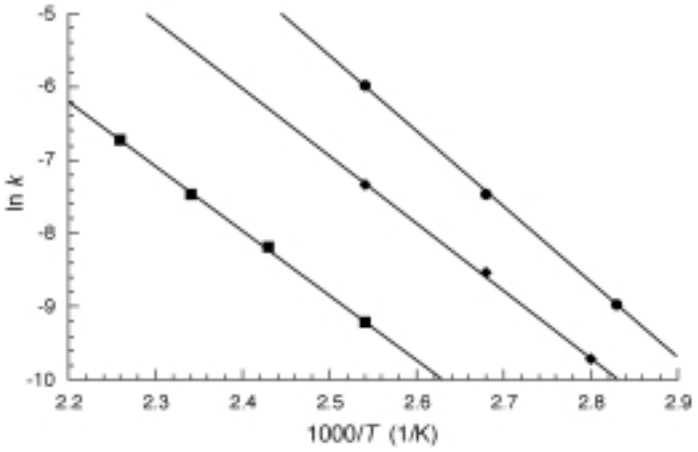

Figure 1. Arrhenius plots for the cycloaromatization of **4** (■), **7** (●), and **8** (◆). The results are summarized in Table 1.

the lactam tautomers will generally cyclize at lower temperatures than the lactim tautomers even though the activation energies do not greatly differ. This was clearly seen since we were able to cyclize **7** and **8** at approximately 80 °C, whereas **4** was very sluggish at the same temperature. Interestingly, the activation energy of **4** is actually the smallest of the three. Since the difference in reactivity cannot be attributed to activation energies, other explanations were sought. One possibility is that the ground state energies of **7** and **8** are lower than **4** so that at the same temperature more molecules of **7** and **8** reach the transition state. Intuitively this is reasonable, since the preferred state of the tautomer under the conditions used here is the lactam. Another possible explanation comes from the entropic term associated with the A values. It is not readily apparent how this term is involved in a unimolecular reaction of this type. A final possibility stems from benzannelation.

It has been shown that the difference in cyclization rates between enediynes and arene diynes is the result of benzannelation.[20] The major factor is that in the cyclization of arenediynes, the intermediate loses less resonance energy when returning to starting materials than the intermediates coming from non-benzoid enediynes. Thus, in the case of arenediynes, retro-cyclization becomes competitive with hydrogen abstraction. The result is that the cyclization of arenediynes can be dependent on the concentration of the trapping agent, while non-benzannelated enediynes are not. However, one must be careful in the strict interpretation of such experiments, since changes in solvent polarity, which can be caused by changing the solvent:traping agent ratio, have also been shown to alter the rate Bergman cycliztion.[21] To examine if benzannelation was important in our system we investigated the CHD concentration-dependent cyclization of **4** and **8**. Only lower concentrations of CHD in DMSO were used to minimize potential solvent effects. The results (Table 2) show that there is no significant dependence on the half-life of either **4** or **8** as a function of CHD concentration. In the case of the O-methyl tautomer **4**, the half-lives were 113.8 ± 6.7 min. Based on previous literature,[20b] more significant differences in rates would be expected. In the case of *N*-methyl **8**, however, the only notable difference was in the initial addition of CHD. This can be explained by the fact CHD is a better radical donor than DMSO. Thus, benzannelation does not seem to be an important factor governing the rate of Bergman cyclization in the pyrimidine–pyrimidone system.

Table 2. Cyclization half-lives ($\tau_{1/2}$) of **4** and **8** as a function of [CHD].

	$\tau_{1/2}$ [min][a]	
[CHD] [nM]	**4**[b]	**8**[c]
0	120.5	99.8
120	114.2	62.4
300	107.1	64.0
600	112.6	59.2

[a] [**4**, **8**] = 6 mM in DMSO with amount of CHD shown. [b] Temp = 120 °C. [c] Temp = 100 °C.

Conclusion

We have found that the rate of Bergman cyclization can be altered by the tautomeric state of the heterocycle into which the double bond is incorporated. The 6- to 25-fold rate enhancement observed for the lactam over the lactim form of uracil–enediyne chimeras is a new example of electronic control of the Bergman cyclization. The activation energies and CHD-dependant cyclization data indicate that ground state effects must be the source of the observed rate differences. These results pave the way for a prodrug approach based on tautomerism. The presence of ten-membered ring enediynes should further accelerate the reaction by raising the ground state energy while maintaining the electronic properties of the tautomers. This should bring the cyclization temperatures into the biological realm, and this work is currently in progress.

Experimental Section

General: All commercial chemicals were purchased from Aldrich, were ACS certified grade, and were used without further purification unless

otherwise noted. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. Chemical shifts are recorded in parts per million on the δ scale referenced to the solvent peak as an internal standard. Melting points are uncorrected.

Kinetics: Kinetic studies were performed by using our previously reported HPLC assay.[15]

5,6-bis(-2-trimethylsilylethynyl) uracil (6): A solution of TMSI (180 mg, 0.9 mmol) in dry CH_2Cl_2 (5 mL) under Ar was added dropwise by syringe to a solution of 2,4-dimethoxy-5,6-bis(-2-trimethylsilylethynyl)pyrimidine (**5**)[15] (100 mg, 0.3 mmol) in dry CH_2Cl_2 (20 mL) at $-78\,^\circ$C. The solution was allowed to warm to room temperature and stirred for three days at that temperature. The reaction was quenched with methanol (5 mL) and washed with 5% aqueous sodium thiosulfate solution. After acidification with 1.6 M HCl (aq), the product was extracted with CH_2Cl_2. The organic layer was dried over anhydrous magnesium sulfate, filtered, and the filtrate evaporated under reduced pressure. Compound **6** (50 mg, 63%) was isolated as a white solid after flash chromatography (EtOAc:hexane, 1:1, v/v). A small amount of starting material was also recovered from the column (11 mg). M.p. 170 °C (decomp); ^{1}H NMR ($CDCl_3$):$\delta = 10.52$ (s, 1H), 10.29 (s, 1H), 0.26 (s, 9H), 0.21 (s, 9H); ^{13}C NMR ($CDCl_3$): $\delta = 162.8$, 150.5, 138.1, 111.8, 103.9, 103.2, 95.3, 94.2, 0.1, -0.7; IR ($CHCl_3$, cm^{-1}): $\tilde{\nu}_{max} = 3397$, 2170, 1695; MS (FAB): *m*/*z*: 305 ([M^+], 100%).

5,6-diethynyl uracil (7): A saturated K_2CO_3-methanol solution (1 mL) was added to **6** (35 mg, 0.12 mmol) in methanol (2 mL). The solution was stirred at room temperature for 2 h, until TLC indicated no remaining starting material. The solution was acidified with HCl-saturated methanol, and compound **7** was isolated by preparative TLC using ethyl acetate as the mobile phase. The product was obtained as a white solid (18 mg, 93%). M.p. 139 °C (decomp); ^{1}H NMR ([D$_6$]DMSO): $\delta = 11.73$ (s, 1H), 11.51 (s, 1H), 5.26 (s, 1H), 4.35 (s, 1H); ^{13}C NMR ([D$_6$]DMSO): $\delta = 162.0$, 149.6, 137.8, 101.5, 93.7, 87.6, 76.0, 74.6; UV (DMSO, nm): $\lambda_{max} = 318.6$, 259.2; IR ($CHCl_3$, cm^{-1}): $\tilde{\nu}_{max} = 3301$, 2122, 1582; MS (FAB): *m*/*z*: 161 ([M^+], 100%).

5,6-Diethynyl-1,3-*N*,*N*-dimethyl uracil (8): K_2CO_3 and methyl iodide were added to **7** (30 mg, 0.19 mmol) in DMF (1 mL) at 0 °C. The solution was stirred for 3 h at 0 °C and for 12 h at room temperature. Water was added to the solution and the product was extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, concentrated under reduced pressure, and subjected to column chromatography (3:7, EtOAc:hexane, v/v) to give compound **8** as a white solid (25 mg, 70%): M.p. 121–122 °C (decomp); ^{1}H NMR ($CDCl_3$): $\delta =$ 4.04 (s, 1H), 3.57 (s, 3H), 3.45 (s, 1H), 3.38 (s, 3H); ^{13}C NMR ($CDCl_3$): $\delta =$ 169.6, 150.5, 138.5, 103.7, 94.1, 84.1, 85.5, 75.4, 73.8, 34.8, 28.6; UV (DMSO, nm): $\lambda_{max} = 324.4$, 259.3; IR ($CHCl_3$, cm^{-1}): $\tilde{\nu}_{max} = 3156$, 2117, 1691; MS (FAB): *m*/*z*: 189 ([M^+], 100%).

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