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Controlling Both Ground- and Excited-State Thermal Barriers to Bergman Cyclization with Alkyne Termini Substitution

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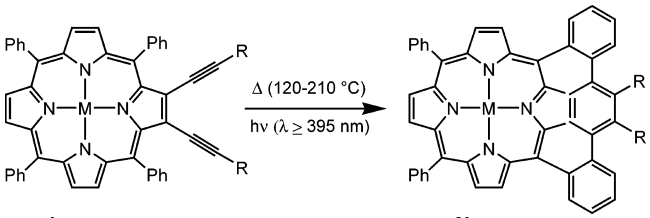
Porphyrins are ubiquitous molecular constructs because of their potential in biomedical applications such as photodynamic therapy[1,2] and the ability to incorporate their electronic properties into optical devices.[3,4] In line with this trend, coupling reactive functionalities into strong porphyrinic chromophores has potential for the development of novel biomedical reagents that can be triggered optically at long wavelengths, without the need for external chemical cofactors.

Attempts to photochemically cyclize simple enediynes[5−9] have been restricted to UV excitation, partially because of the lack of a suitable chromophore with extinction in the visible spectral region. In addition, traditional acyclic enediynes are generally more difficult to activate than their carbocyclic[10] or metallocyclic[10,11] counterparts, exhibiting restrictively high activation barriers. This work focuses on modulating thermal and photochemical activation barriers of porphyrinic enediynes.

The cross-coupling reaction of 2,3-dibromo-5,10,15,20-tetraphenylporphyrin with the corresponding organostannanes in the presence of Pd^0 catalyst in THF at reflux temperature yields free base 2,3-dialkynylporphyrins **1a**,**c**−**e** (Scheme 1).[12−14] The subsequent deprotection of trimethylsilyl group of **1a** with TBAF in THF under aqueous conditions produces the 2,3-diethynyl-5,10,15,20-tetraphenylporphyrin **1b** in 87% yield.[13] Compounds **1a**−**d** undergo zinc insertion upon treatment with $Zn(OAc)_2 \cdot 2H_2O$ in $CHCl_3$/MeOH to give zinc(II) 2,3-dialkynyl-5,10,15,20-tetraphenylporphyrins (**2a**−**d**) in 70−92% yields (Scheme 1).

Scheme 1. Dialkynylporphyrinic Enediynes and Their Bergman Cyclization Reactivities



The crystal structure of **1c** (Figure 1) reveals a near-planar porphyrin backbone with an alkyne termini distance (C24···C24A) of 3.658 Å. To assess the thermal reactivities of **1a**−**e** and **2a**−**d**, thermal Bergman cyclization temperatures have been evaluated in solid state by differential scanning calorimetry (DSC). Single exotherms are observed for each compound over a wide range of temperatures (**1b**: 160 °C; **1a**: 388 °C), indicating a substantial difference in the activation barriers to Bergman cyclization within the series. For R = H and R = Ph, sharp exotherms are observed ∼100 °C apart (**1c**: 257 °C; **2b**: 172 °C; **2c**: 272 °C), revealing a dependence of cyclization reactivity on the steric bulk of the R-group. Thermal Bergman cyclization of **1a**−**e** and **2a**−**d** was also studied in chlorobenzene and ∼35-fold 1,4-cyclohexadiene at

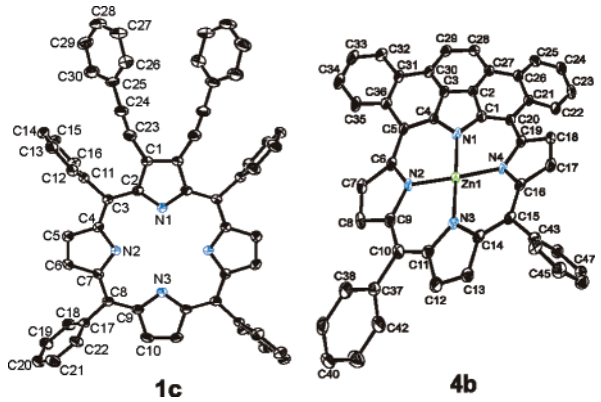


Figure 1. X-ray structure of **1c** and **4b** (from photoreaction of **2b**). Thermal ellipsoids are illustrated at 50% probability.

Table 1. Thermal Bergman Cycloaromatization of **1a**−**e** and **2a**−**d**

compounds	reaction conditions	**1**[a] or **2**[a] (%)	**3**[b] or **4**[b] (%)
1a: R = TMS	C_6H_5Cl, CHD, 190 °C, 24 h	95	−
1b: R = H	C_6H_6, *i*PrOH, 25 °C, 72 h	98	−
1b: R = H	C_6H_5Cl, CHD, 120 °C, 8 h	−	65
1c: R = Ph	C_6H_5Cl, CHD, 200 °C, 30 h	30	50
1d: R = Pr	C_6H_5Cl, CHD, 160 °C, 24 h	−	55
1e: R = *i*Pr	C_6H_5Cl, CHD, 190 °C, 24 h	10	60
2a: R = TMS	C_6H_5Cl, CHD, 190 °C, 24 h	96	−
2b: R = H	C_6H_5Cl, CHD, 120 °C, 8 h	−	70
2b: R = H	C_6H_6, *i*PrOH, 50 °C, 72 h	92	6
2b: R = H	C_6H_6, *i*PrOH, 25 °C, 72 h	96	−
2c: R = Ph	C_6H_5Cl, CHD, 210 °C, 30 h	60	30
2d: R = Pr	C_6H_5Cl, CHD, 160 °C, 24 h	40	45

[a] Recovered starting compounds **1a**−**e** or **2a**−**d**. [b] Isolated yields of cyclized products **3b**−**e** or **4b**−**d**.

120−210 °C (Table 1). Compounds **1b** and **2b** react at lower temperature (120 °C) and produce cyclized products **3b** and **4b** in higher yields (65−70%) than their propyl, isopropyl, and phenyl analogues, with R = Ph being the most stable. Continuing in this trend, the −TMS derivatives **1a** and **2a** exhibit no reactivity even after heating at 190 °C in chlorobenzene/CHD for 24 h.

The conjugated porphyrin−enediyne framework is ideal for determining whether electronic excitation of the chromophore is capable of activating a relatively stable, acyclic enediyne unit. Photolysis (at $\lambda \geq 395$ nm) of **1b** and **2b** at 10 °C leads to the formation of isolable picenoporphyrin products in 15 and 35% yields, respectively, in 72 h, whereas these compounds are stable under identical conditions in the dark at 25 °C (Table 2).

The crystal structure of photoproduct **4b** (Figure 1) displays a mixed ruffle/saddle distorted porphyrin fused to a planar piceno unit.[12−14] Remarkably, the formation of Bergman cyclized product **4b** from acyclic enediyne **2b** is not restricted to high-energy photoexcitation. Rather, photolysis of **2b** at 10 °C at longer

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Table 2. Photo-Bergman Cycloaromatization of **1** and **2**[a]

compounds	reaction conditions	**1b**[b] or **2b**[b] (%)	**3b**[c] or **4b**[c] (%)
1b: R = H	C_6H_6, *i*PrOH, 10 °C, $h\nu$ ($\lambda \geq 395$ nm), 72 h	45	15
2b: R = H	C_6H_6, *i*PrOH, 10 °C, $h\nu$ ($\lambda \geq 395$ nm), 72 h	35	35
2b: R = H	C_6H_6, *i*PrOH, 10 °C, $h\nu$ ($\lambda \geq 515$ nm), 72 h	65	15
2b: R = H	C_6H_6, *i*PrOH, 10 °C, $h\nu$ ($\lambda \geq 590$ nm), 120 h	85	6

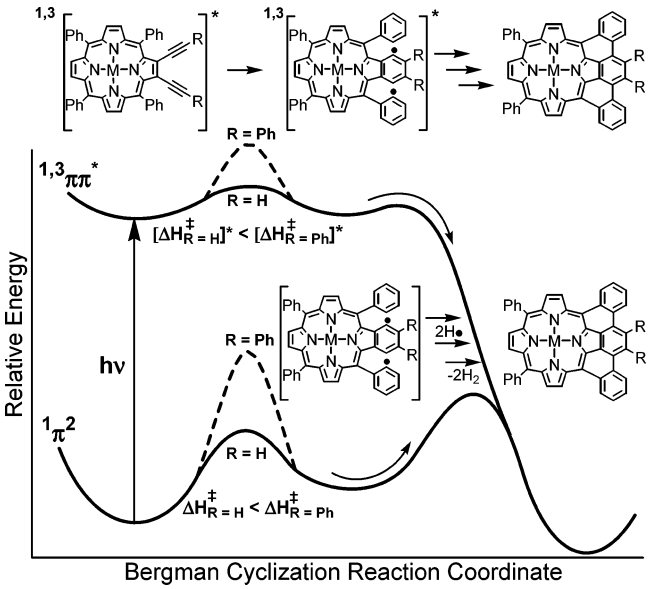
[a] Photo-Bergman cyclization of **1a**,**c**−**e**, **2a**,**c**,**d** (entries 1, 4−7, 11, and 12 in Table 1) was attempted in benzene/*i*PrOH at 10 °C with $\lambda \geq 395$ nm light for 72 h, but starting material was recovered quantitatively. [b] Recovered starting material. [c] Isolated yields of cyclized product.

wavelengths ($\lambda \geq 515$ or 590 nm) in benzene/*i*PrOH (4:1, 72 h) produces **4b** in 15 and 6% isolated yields, respectively. Photolyses of **1a**,**c**−**e** and **2a**,**c**,**d** were also performed under the same reaction conditions, but in all cases, starting material was recovered in quantitative yield.

To probe whether the activation barriers to Bergman cyclization in the excited state follow the same trend as those in the ground state, photolyses of **1c** and **2c** were performed at elevated temperature (125 °C). Unlike thermolysis at 125 °C, which did not yield Bergman cyclized product for R = Ph, photolysis generates small amounts of picenoporphyrin (**3c**: 5%; **4c**: 8% based on ^{1}H NMR) as well as a mixture of reduced porphyrin products that were not separable. While some photoproduct was formed at elevated temperature, compounds **1c** and **2c** with R = Ph are still considerably more stable than **1b** and **2b** with R = H, which leads to photoproduct in up to 35% yield at 10 °C. Thus, trends in the barriers to the Bergman cyclization step in the excited state have similar relationships to those in the ground state (from DSC and product isolation) as a function of the R-group.

The picture that emerges from this work is shown in Scheme 2.

Scheme 2. Reaction Profile for Ground- and Excited-State Bergman Cyclization of **1b**−**c** and **2b**−**c**



Thermolysis along the ground-state potential surface leads to generation of the typical 1,4-phenyl diradical intermediate presumed to be singlet in origin.[15] In the presence of H-donor, a subsequent activated process leads to production of picenoporphyrin by radical addition to the adjacent *meso*-phenyl rings and subsequent rearomatization by loss of H_2.[12−14] The latter step is rate limiting for R = H,[13] but the high temperature of the R = Ph cyclization reaction[12] suggests that it is not for R = Ph. The pronounced dependence of the reaction on R reveals that the barrier to the 1,4-diradical intermediate is smaller for R = H than that for R = Ph ($\Delta H_{R=H}^{\ddagger} < \Delta H_{R=Ph}^{\ddagger}$) and is therefore controlled at least in part by the steric bulk of the R-group at the alkyne termini. This is supported by computational studies that suggest a ∼15 kcal/mol difference in $\Delta G^{\ddagger}$ for such a substitution.[16] Similarly, photoexcitation into the Soret and Q-bands populates the $^1\pi\pi^*$ manifold, ultimately leading to formation of Bergman product in respectable yields for R = H (35% at 10 °C) and in trace amounts for R = Ph at 125 °C, once again reflecting differential activation barriers as a function of R-group ($[\Delta H_{R=H}^{\ddagger}]^* < [\Delta H_{R=Ph}^{\ddagger}]^*$). In this case, cyclization can occur along either the excited singlet or triplet surface via an excited diradical species,[8,17,18] the subsequent intermediates derived from which remain unclear. It is important to highlight that $[\Delta H_{R=H}^{\ddagger}]^* < \Delta H_{R=H}^{\ddagger}$ and $[\Delta H_{R=Ph}^{\ddagger}]^* < \Delta H_{R=Ph}^{\ddagger}$, which reveals that in addition to having the same energetic relationships in the ground and excited states, the thermal barriers in the excited states are lower than those in the ground states overall. Finally, conjugation of the enediyne unit into the porphyrin electronic transitions leads to sufficient distortion to not only generate photoproduct with $\lambda \geq$ 395 nm (Soret) excitation, but with longer wavelength, Q-band excitation ($\lambda \geq 515$, 590 nm) as well. This suggests that it may be possible to extend photoelectronic activation of enediynes well out into the visible spectral region, enhancing the potential for such frameworks as photodynamic therapy agents in hypoxic environments.

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Supporting Information Available: Experimental details and characterization data for **1c**−**e**, **2a**−**d**, **3b**−**d**, and **4b**−**d** as well as X-ray crystallographic data for **1c** and **4b** (PDF, CIF, plain text). This material is available free of charge via the Internet at http://pubs.acs.org.

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