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Spin-state control of thermal and photochemical Bergman cyclization[†][‡]

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Thermal Bergman cyclization of Pt(II) dialkynylporphyrins reveals a marked reduction in the cyclization temperature relative to the free base and Zn(II) derivatives. In contrast, photogenerated ${}^{3}\pi\pi^{*}$ population produces no detectable Bergman photocyclization, suggesting that the photoreactivities of the related free base and Zn(II) derivatives occurs *via* the ${}^{1}\pi\pi^{*}$ state.

Porphyrinoids have a rich electronic excited state history that has been exploited for Photodynamic Therapy (PDT).¹ A limitation of this technology is the diffusion-controlled requirement of the diradical species, ³O₂. Photoinduced triplet–triplet annihilation converts the ³ $\pi\pi^*$ state of the porphyrinoid to ground state, with concomitant generation of ¹O₂. Since solid tumors experience decreased oxygen levels, PDT as a treatment modality is not effective. However, radical-generating functionalities coupled to the porphyrins have potential as advanced PDT agents for such hypoxic environments as they maintain red spectral region photoactivation, while alleviating the need for external chemical cofactors.

Photochemical Bergman cyclization of dialkynylporphyrins has paved the way for just such reagents if the outcome can be both controlled and optimized. Within this theme, our group demonstrated that the free base and Zn(II) 2,3-diethynyl-5,10,15,20-tetraphenylporphyrins could be photocyclized and trapped using the *meso*-phenyl ring addition at visible wavelengths in yields as high as 35%.² Since for free base and Zn(II) tetraphenylporphyrins, ${}^{1}\pi\pi^{*}$ excited-state lifetimes of 2–12 ns and ${}^{3}\pi\pi^{*}$ state lifetimes of micro-to-milliseconds are the rule,³ it is unclear through which of the two excited states this reaction occurs. Experimentally, Turro *et al.* demonstrated that singlet excitation leads to Bergman product while triplet-state photosensitization produces mainly alkyne-reduced species.⁴ Computational analyses of simple enediynes⁵ support these observations by demonstrating that while singlet excitation leads to formation of the 1,4-diradical intermediate, triplet state population promotes out-of-plane distortions about the double bond for simple enediynes, as well as in-plane distortions at the terminal carbon for aromatic enediyne systems.⁶ These distortions are consistent with *cis-trans* isomerized photoproducts⁷ and reduced alkyne species formed upon bimolecular excited triplet state sensitization.

The premise of this work is to determine if inserting the heavy atom Pt(π) into the porphryin core can *unimolecularly* affect the Bergman cyclization of dialkynylporphyrins. Pt(π) porphyrins are known to facilitate rapid intersystem crossing and exhibit the ${}^{3}\pi\pi^{*}$ state.⁸ Base Pt(π) porphyrins exhibit markedly quenched ${}^{1}\pi\pi^{*}$ lifetimes (\leq 15 ps) and ${}^{3}\pi\pi^{*}$ long-evities of >1 μ s.⁹ Thus, understanding the specific state that effectively produces the Bergman product will enhance H-atom abstraction efficiency from potential biological substrates.

The synthesis of free base, $Zn(\pi)$, and $Ni(\pi)$ 2,3-ethynyl-5,10,15,20-tetraphenylporphyrins were previously reported.^{2,10} To insert Pt(π), 10 equiv. of Pt(acac)₂ are complexed to dry benzonitrile under N₂ at 190 °C for 30 min (Scheme 1).



Scheme 1 Synthesis of the Pt(II) series of porphyrins 1-3.

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The solution is cooled for 10 min, transferred into a solution of 2,3-dibromo-5,10-15-20-tetraphenylporphyrin in benzonitrile and reacted at 190 °C for an additional 6.5 h. The crude product is purified by activated neutral aluminum oxide column chromatography to give (2,3-dibromo-5,10-15-20-tetraphenylporphyrinato)platinum(II) (1) in 88% yield. Ethynyl units are installed by treating 1 with three equivalents of trimethyl-(trimethylstannylethynyl)silane, dry THF, and a Pd(0) catalyst in an inert atmosphere and refluxed at 70–80 °C for 6 h. The (2,3,-bis[trimethylsilylethynyl]-5,10,15,20-tetraphenylporphyrinato)platinum(II) (2) is isolated in 58% yield. Compound 2 is deprotected at RT with 3 equivalents of a 1 M solution of tetrabutylammoniumfluoride (TBAF) in THF for 1.5 h to afford (2,3-diethynyl-5,10,15,20-tetraphenylporphyrinato)platinum(II) (3) in 40% yield.

Crystals suitable for X-ray analysis for three of the Pt(II) porphyrins were obtained by slow evaporation of a 1 : 1 methanol–dichloromethane solution. Attempts to obtain the structure of (2,3-diethynyl-5,10,15,20-tetraphenylporphyrinato) platinum(II) **3** were unsuccessful. Instead, the Bergman product (10,15-diphenyl-piceno[20,1,2,3,4,5*fghij*]porphyrinato)platinum(II) **4** crystallized from this ambient temperature solution after one week.

The thermal Bergman cyclization reactivity of 3 is intriguing. Differential scanning calorimetry (DSC) of 3 shows an exothermic peak at 140 °C compared to 160 °C for the free-base and Zn(II) derivatives.² The reduced temperature and broadened nature of the peak indicate that the activation barrier for this Pt(II) dialkynylporphyrin is markedly lower than the free base and Zn(II) dialkynylporphyrins. This same reactivity profile translates to solution (Table 1). Thermal cyclization studies of 3 show Bergman reactivity at a lower solution temperature than any known H-terminated, porphyrinic-enediynes. For comparison, the free base derivative cyclizes at 120 °C in 8 hours, resulting in the picenoporphyrin in 65% yield.² The same reaction conditions for the Zn(II) derivative gives the cyclized compound in 70% yield. However, thermolysis of 3 proceeds to completion at 115 °C after only 2 hours, producing picenoporphyrin 4 in 45% yield, but with complete consumption of starting material (Scheme 2). Higher yields are achieved at lower temperature and shorter reaction times, but those reactions do not go to completion.

Longer reaction times also result in a larger amount of side product, regardless of reaction temperature (Table 1). The best yields of the cyclized product result from a reaction time of 2 h at 95 °C, which produces 60% yield of the target compound and 36% of remaining starting material, a total material

Table 1 Reaction conditions for the thermal Bergman cyclization of $\mathsf{Pt}({\scriptscriptstyle \textsc{i}})$ porphyrins

Alkyne terminus	Reaction conditions	ST^{a} (%)	$\operatorname{Cyc}^{b}(\%)$
Н	Toluene, 60 °C, 4 h	38	34
Н	Toluene, 80 °C, 1 h	50	40
Н	Toluene, 95 °C, 1 h	50	47
Н	Toluene, 95 °C, 2 h	36	60
Н	Toluene, 115 °C, 2 h	_	45
TMS	Toluene, 190 °C, 24 h	64	_
TMS	Toluene, 150 °C, 24 h	92	_

^a Recovered starting compounds. ^b Isolated yields of cyclized products.



Scheme 2 Thermal Bergman cyclization of **3** leads to the cyclized **4** in 21–60% yields, but photolysis results only in starting material.



Fig. 1 Electronic absorption spectra of the Pt(II) porphyrins 1-4

recovery of 96%. On the low temperature side, **3** cyclizes as low as 60 °C over 4 h and gives the picenoporphyrin compound in 34% yield, with 38% of the starting material recovered. The extended reaction time creates polymeric side products which are not separable and likely derive from oligomerization.

Representative electronic absorption spectra for the Pt(II) porphryins are shown in Fig. 1. The absorption spectra for the alkynylated compounds 2 and 3 are bathochromatically shifted from the Pt(II)-dibromoporphyrin 1 due to the increased delocalization of aromaticity caused by the additional triple bonds. The electronic spectrum of the TMS-protected derivative 2 is slightly more red-shifted than the deprotected product, with the B-band at $\lambda = 418$ nm ($\varepsilon = 2.35 \times 10^5$ M⁻¹ cm⁻¹) and Q-bands at $\lambda = 524$ and 564 nm ($\varepsilon = 2.28 \times 10^4$ and $\varepsilon = 2.35 \times 10^4$ M⁻¹ cm⁻¹, respectively). Similarly, the B-band of 3 lies at $\lambda = 414$ nm ($\varepsilon = 2.26 \times 10^5$ M⁻¹ cm⁻¹), with the Q-bands at 521 and 560 nm ($\varepsilon = 1.93 \times 10^4$ and $\varepsilon = 1.73 \times 10^4$ M⁻¹ cm⁻¹, respectively), reflecting a comparable π -delocalization pathway.

In contrast, benzannulation and *meso*-phenyl ring quenching of the diradical intermediate results in an extension of π -delocalization, and a corresponding red-shift of the electronic spectrum. The B-band of **4** is now detected at $\lambda = 440$ nm ($\varepsilon = 1.16 \times 10^5 \text{ M}^{-1} \text{ cm}^{-1}$), and the two Q-bands lie at $\lambda = 603$ and 611 nm ($\varepsilon = 3.28 \times 10^4$ and $\varepsilon = 3.76 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$, respectively). It is known that addition of fused benzene rings break the accidental degeneracy of the $1a_{1u}$ and $1a_{2u}$ HOMO set. This relaxes the ideal forbidden/allowed characters of the Q/B transitions causing the Q-bands to gain intensity at the expense of the B-band.¹¹

Remarkably, 3 also undergoes spontaneous Bergman cyclization on the benchtop at ambient temperature, which was revealed by the X-ray structure of 4 from a 1:1 methanol-dichloromethane solution. To probe whether the room temperature reaction was thermal, photoelectronic, or photothermal, three vials containing



Fig. 2 Electronic absorption of the three samples of **3** and the cyclized **4** over 30 days, under N₂, normalized to $\lambda = 415$ nm. vial 1 was kept at RT on the benchtop, vial 2 was kept at RT in the dark, and vial 3 was kept at -20 °C in the dark.

the same concentration of **3** in DCM were prepared. One vial was left on the benchtop (light + RT), one vial was placed in a drawer (dark + RT), and one shielded from light and placed in the freezer at -20 °C (dark + cold). A vial of the same concentration of a control, (2,3,-bis[trimethylsilylethynyl]-5,10,15,20-tetraphenylporphyrinato)platinum(II) **2** was also left on the benchtop. The four solutions were monitored by TLC and electronic absorption spectroscopy for 30 days (Fig. 2). A green product indicative of the cyclized **4** appears after 4 days from the light + RT vial, and after 6 days from the dark + RT vial. Over 30 days, no **4** develops in the dark + cold vial.

The electronic spectra for the bench-top cyclization experiments show gradual growth at $\lambda = 600$ and 613 nm, indicative of the Pt(II) picenoporphyrin **4**. For vial 1 (light + RT), these transitions can be observed after 7 days, and continuously increase throughout the 30-day period. In vial 2 (dark + RT), the same features are evident after 7 days, although to a lesser extent. The $\lambda = 613$ nm band becomes prominent midway through the 30-day evaluation and persists. In contrast, vial 3 shows no red-shifted absorption features, even after 30 days.

The photochemical contribution to this reaction in absence of thermal energy was then evaluated by placing 5 mg of 3 in a quartz Schlenk flask with 100 mL dry and degassed toluene, and irradiated with a $\lambda \geq 395$ nm cutoff filter for 72 hours at 10 °C. No cyclized product 4 is formed as 96% of the starting material is recovered. Previous work by Nath *et al.*² showed that the free base and Zn(II) derivatives of the dialkynylporphyrin produce cyclized products in 15 and 35% yields, respectively, under these conditions. Photolytic controls of the TMS derivative 2 and picenoporphyrin 4 result in quantitative recovery of starting material. When the cooling bath was removed during photolysis of 3, photothermal heating raised the solution temperature to 30 °C over 72 h, and cyclized 4 was isolated in 21%. Heating of 3 in the dark to 30 °C for 72 h also produces 4 in comparable 12% yield, indicating that this is indeed a thermally-induced reaction.

Consistent with this picture is the kinetic evolution of transient absorption spectra of 3 following $\lambda = 476$ nm excitation in degassed benzonitrile (ESI[‡]). The spectral profile exhibits a classic excited-state Soret absorption maximum at $\lambda = 471$ nm, a weaker, tailing feature beyond 600 nm, and ground-state bleaching at $\lambda = 530$ nm and 565 nm. These are commensurate with Pt(II) tetraphenylporphyrin transient absorption markers resulting from electron promotion

within the π -manifold. The kinetic evolution of these features are synchronized and decay with $\tau = 5.7 \,\mu s \,(\lambda = 476 \,nm)$, which confirms the identity of this long-lived state as ${}^{3}\pi\pi^{*}$ in origin as Pt(II) porphyrins are known to be non-fluorescent and have ${}^{1}\pi\pi^{*}$ lifetimes of ≤ 15 ps.⁹ Since the long-lived ${}^{3}\pi\pi^{*}$ is correlated with the absence of photoelectronic reactivity of 3, the cyclization may be spin-state regulated as the corresponding free base and Zn(II) dialkynylporphyrins are both photochemically active and their base TPP frameworks have 2–12 ns ${}^{1}\pi\pi^{*}$ lifetimes.³ Thus, despite the more facile thermal reactivity of the Pt(II) analogue 3, ${}^{3}\pi\pi^{*}$ population makes the photoelectronic cyclization pathway less viable. That no triplet photoproduct is observed from this reaction may be system and condition specific. The significant steric bulk in the vicinity of the alkynes may help impede ${}^{3}\pi\pi^{*}$ state-preferred bond reduction.^{4,6} Additionally, the longer photolysis wavelength, and to a lesser extent the diminished energy of the ${}^{3}\pi\pi^{*}$ state, may also preclude significant formation of triplet-induced photoproducts observed of high-energy photolysis of less conjugated enediynes.⁴

The thermal Bergman cyclization reactivity of Pt(II) dialkynylporphyrins reveals a surprising reduction in the temperature at which the picenoporphyrin product is formed relative to the free base and Zn(II) derivatives. In contrast, photoexcitation leads to no detectable photoelectronic Bergman cyclization. Transient absorption confirms the kinetically competent photoexcited state as ${}^{3}\pi\pi^{*}$ in nature, suggesting that this surface is less viable for the photo-Bergman event, despite the facile ground-state thermal reactivity. These results suggest that the photoreactivities of the free base and Zn(II) derivatives occur *via* the ${}^{1}\pi\pi^{*}$ state, thereby demonstrating spin-state selectivity of the photo-Bergman reaction for these systems, and thus potential utility in advanced PDT for hypoxic environments.

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