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Accelerated Bergman cyclization of porphyrinic-enediynes†

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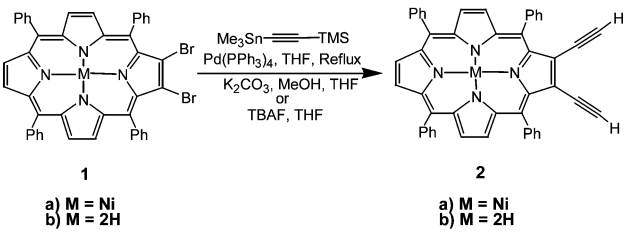
The Bergman cyclization of simple diethynylporphyrinic-enediynes exhibits a double activation barrier to the formation of Bergman cyclized product. Addition of H-atom acceptor accelerates the formation of the picenoporphyrin, indicating that the second barrier is rate limiting.

Our interests in activation of enediyne frameworks toward Bergman cyclization[1] and the formation of the reactive 1,4-phenyl diradical intermediate[2–4] led us to probe the syntheses and reactivities of conjugated enediyne constructs.[5] Recently, Smith *et al.* showed that conjugated porphyrin-enediynes could be prepared in good yields and would thermally cyclize to generate substituted Ni-picenoporphyrin derivatives.[6] The proposed mechanism for this unusual self-quenching reaction involves a tetrahydro intermediate that must lose 2 moles of H_2 to promote aromatization to the Ni-picenoporphyrin product. The atypical mechanistic intermediate, coupled with the quantitative recovery of the –TMS starting material upon thermal activation, further prompted our interests in whether the activation barrier to product formation was governed in part by the loss of H_2, as well as the usual contributions to Bergman cyclization such as steric strain in the transition states[7] and products, as well as the alkyne termini separation.[8,9]

To address these issues, we have prepared Ni(II) and free base 2,3-diethynyl-5,10,15,20-tetraphenylporphyrins with –TMS or –H at the alkyne termini positions† using the method reported by Smith *et al.* (Scheme 1).[6]

Reaction of the Ni(II) or free base (2H) 2,3-dibromo-5,10,15,20-tetraphenylporphyrin[10] (**1a,b**) with Me_3Sn–≡–TMS (TMS = trimethylsilyl) over a Pd(0) catalyst,[11] and subsequent deprotection with base under aqueous conditions yields the 2,3-diethynyl-5,10,15,20-tetraphenylporphyrin, **2a,b**.

The X-ray structures of **2a,b** (Fig. 1) show that the Ni(II) derivative is highly distorted and adopts a mixed ruffled/saddled conformation,[12] while the free base analogue is relatively planar, exhibiting only a modest mixed ruffle/saddle distortion which removes the coplanarity of the alkyne termini carbons. These conformations lead to room temperature stable structures with solid-state Bergman cyclization temperatures of 172 and 160 °C, respectively, as measured by differential scanning calorimetry.



Scheme 1 Synthesis of diethynylporphyrinic-enediyne **2a,b**.

† Electronic supplementary information (ESI) available: syntheses, characterization of **2a–4b**, crystallographic files (CCDC 200680–200685) in CIF format. See http://www.rsc.org/suppdata/cc/b2/b212923j/

The high thermal barrier to the Bergman cyclized picenoporphyrin product of **2a** in solution reported by Smith *et al.* (190 °C, 8 h)[6] seemed contrary to the general empirical relationship between DSC temperature and solution-state Bergman cyclization in simple metalloenediyne structures.[2–5,9] Moreover, heating of **2a,b** in MeOH/$CHCl_3$ over a wide temperature range (25–80 °C) gives very sluggish reactivity with small (< 5%) and nearly constant product yield. These factors suggested that cycloaromatization may not be the high barrier step in picenoporphyrin product formation. Rather, loss of H_2 (or 2H·) could be inhibiting product formation.

Addition of 2 equiv of the $2e^-/2H^+$ acceptor DDQ (DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone) to **2a,b** at room temperature in $CHCl_3$/MeOH (2:1) yields picenoporphyrin products **3a,b** in 30–40% yield within 30 min (Scheme 2) with no additional heating.

The green products **3a**[6] and **3b**, are straightforwardly detected in solution by ^{1}H NMR. For **3b**, a diagnostic resonance from the two protons of the new Bergman cyclized ring appear at δ = 8.93, while those of the modified *meso*-phenyl rings are detected as distinct doublets at δ = 8.91 and 9.56 ppm, a triplet at 7.91 ppm, as well as a convoluted triplet at 7.76 ppm. In addition, the electronic absorption spectrum of **3b** (CH_2Cl_2) is markedly red-shifted from that of **2b** exhibiting a Soret band with λ_{max} = 459 nm, and four distinct Q-bands at λ_{max} = 600, 622, 649, and 684 nm, thereby confirming the increase in π-

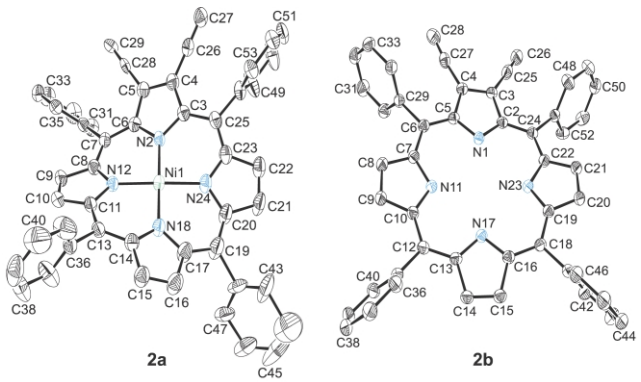
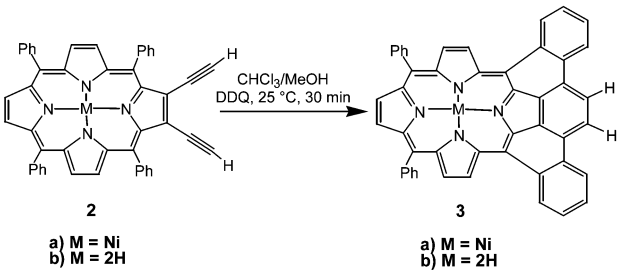


Fig. 1 X-Ray structures of **2a,b**. Alkyne termini separation **2a**: C27···C29 = 4.44 Å; **2b**: C26···C28 = 4.09 Å. Thermal ellipsoids are illustrated at 50% probability.



Scheme 2 Bergman cyclization of **2a,b** in the presence of DDQ to generate picenoporphyrins **3a,b**.

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conjugation in **3b**. Formation of picenoporphyrin products **3a,b** have also been confirmed by X-ray crystallography (Fig. 2). The structure of **3a**[6] exhibits a planar piceno unit within a strongly ruffled porphyrin backbone. In contrast, the structure of **3b** is nearly planar, with only a modest ruffle distortion.

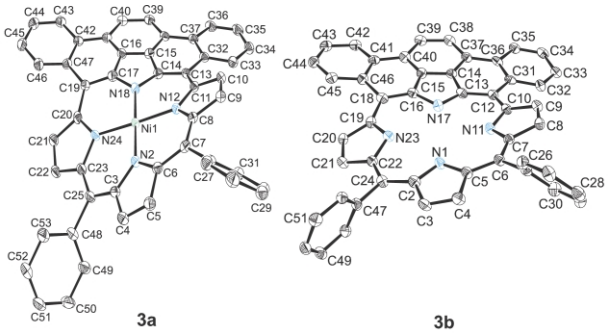


Fig. 2 X-ray structures of **3a,b**. Thermal ellipsoids are illustrated at 50% probability.

The –TMS derivatives (**4a,b**) can also be prepared by reaction **1a** or **1b** with (trimethylsilylacetylene)trimethylstannane as that shown for the preparation of **2a** prior to deprotection.[6] The X-ray structure of **4a** once again exhibits a mixed ruffled/saddled distortion, while **4b** is generally planar with only a modest out-of-plane projection of the alkynes from the ring in a *syn*-configuration (Fig. 3). The alkyne termini separations are very similar, indicating that the conformation of the porphyrin has a modest effect, in these cases, on the disposition of the enediyne unit.

Heating of **4a,b** in the solid-state reveals strong exothermic peaks in the DSC traces at 332 and 388 °C. For **4a**, this feature is immediately preceded by a melting endotherm, indicating a change of state and negating the ability to compare these temperatures directly.

Reaction of **4a** in $CHCl_3$/MeOH in the presence of DDQ at 25 °C for 24 h reveals a slow decomposition of the starting material without detectable formation of picenoporphyrin product. These results are in contrast to those observed upon reaction of **2a,b** with DDQ under the same conditions. This comparison, coupled with the high DSC temperatures for **4a,b**, and the inability to obtain picenoporphyrin product in solution at accessible temperatures from **4a** alone,[6] reflect an increased activation barrier to Bergman cyclization for **4a,b** due at least in part to the steric crowding of the –TMS functionalities in the product.

The observation that DDQ greatly enhances generation of **3a,b** without detection of an intermediate is in agreement with, but not identical to the mechanism proposed by Smith *et al.* involving formation of the quasi-stable tetrahydro intermediate *via* H-atom donation by 1,4-cyclohexadiene.[6] This species

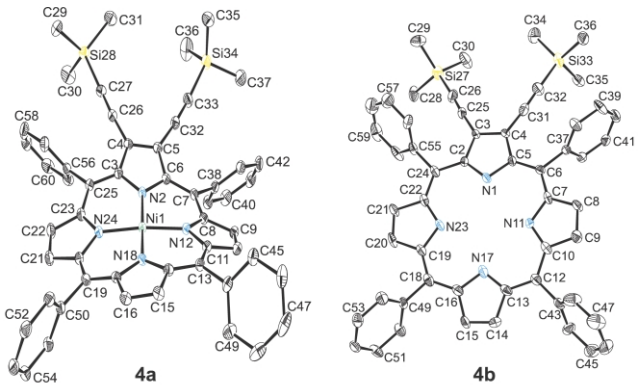
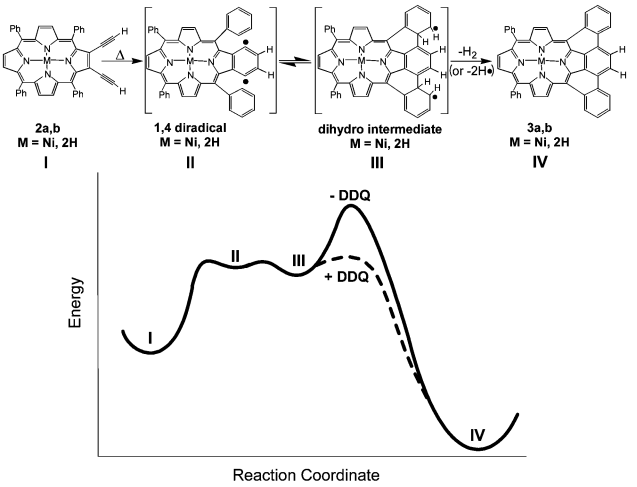


Fig. 3 X-ray structures of **4a,b**. Alkyne termini separation **4a**: C27···C33 = 4.19 Å; **4b**: C26···C32 = 4.16 Å. Thermal ellipsoids are illustrated at 50% probability.

subsequently must lose 2 moles of H_2 (or 4 H•) to rearomatize to the picenoporphyrin product. Since under our solution conditions ($CHCl_3$/MeOH) in the absence of DDQ, only starting material and product are observed by NMR up to 85 °C, a more highly reactive intermediate than the tetrahydro species (*e.g.* dihydrodiradical, **III**, Scheme 3) must be in equilibrium with starting material in the absence of DDQ. It is clear that the H-atom donor ability of the solution may be influencing the intermediate *en route* to picenoporphyrin product.



Scheme 3 Illustration of the influence of DDQ on the proposed porphyrinic-enediyne-picenoporphyrin reaction coordinate.

The ability to generate Bergman cyclized product in 30–40% yield under ambient conditions in the presence of DDQ suggests that the primary reaction coordinate for picenoporphyrin product formation can be divided into at least two sequential steps with two significant activation barriers: 1) a Bergman cyclization and radical addition reaction, and 2) a hydrogen loss/rearomatization step (Scheme 3). In light of the poor yield of product in the absence of DDQ, the Bergman cyclization/addition step must be facile, but contain a rapid equilibrium between the proposed intermediate and starting material as the tetrahydro species is not detected under our conditions. This also suggests that the second step is product limiting, and that the activation barrier for loss of hydrogen is greater than that for the Bergman cyclization/addition step. From a biological perspective, the ability of external substrates or reactants to drive Bergman cyclization reactions to completion suggests that environmental factors may be important for modulating enediyne reactivity under varying solution conditions.

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