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COMMUNICATION

Intramolecular hydrogen bonding as a synthetic tool to induce chemical selectivity in acid catalyzed porphyrin synthesis†‡

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A straightforward procedure based on the formation of intramolecular hydrogen bonds to impart selectivity in the preparation of multi-functionalized porphyrins has been developed. To illustrate the concept, the synthesis of a biomimetic artificial photosynthetic model able to undergo electron and proton transfer reactions upon irradiation is reported.

The rich chemical and spectroscopic properties of porphyrins have prompted their study and application across many scientific fields. Much of this popularity is due in large part to the development of relatively efficient and specific synthetic protocols that allow for the preparation of a huge number of functionalized porphyrin molecules.[1] As a result, complex nanostructures composed of porphyrin subunits, such as large multiporphyrin arrays,[2a–d] polymers,[2e–g] dendrimers,[2h,i] mechanically-linked systems,[2j–l] and molecular machines,[2m,n] have been reported. In the field of artificial photosynthesis, porphyrins offer useful alternatives to the synthetically demanding and relatively unstable chlorophylls found in nature, and have been extensively investigated as components of antenna devices and reaction center models.[3]

The formation of a porphyrin molecule typically involves a condensation reaction between pyrrole and aldehyde derivatives in organic solvent, at room temperature, and under acid catalysis.[4a–c] Despite the mild conditions, this protocol is not compatible with some functional groups. For example, formyl, phenol, amine, terminal ethynyl, carboxylic acid, and acyclic acetal functionalities fail to afford porphyrins under the classical conditions.[4c] The formation of porphyrins containing such groups usually requires the use of protecting groups or further synthetic elaboration of suitable porphyrin precursors. However, these strategies render the synthesis longer and inefficient. In cases where multi-functionalized porphyrins are required, the synthesis becomes challenging if not impossible.

One particular example in this regard comes from our own work. In our efforts[5a,b] to gain insight into the photophysics of Photosystem II (PSII), we have designed biomimetic artificial photosynthetic models able to undergo electron transfer (ET) and proton-coupled electron transfer (PCET) reactions that mimic the photo-redox processes occurring between the primary electron donor chlorophyll complex (P_{680}) and the Tyrosine$_z$-Histidine-190 pair (Tyr$_z$-His190).[6] In one of our designs (Fig. 1), a high-potential 5,15-*bis*(pentafluorophenyl)-porphyrin (PF_{10}, the primary electron donor) bears a benzoic acid functionality (for attachment of the complex to a TiO_2 nanoparticle, which serves as the primary acceptor) and a 2-(2′-hydroxyphenyl)benzimidazole (Bi-PhOH) group (the secondary electron donor). The Bi-PhOH moiety is specifically designed to feature an intramolecular hydrogen bond between the phenolic oxygen and the nitrogen lone pair of the benzimidazole residue, such that the oxidation of the phenol occurs with the transfer of the phenolic proton to the benzimidazole residue (Fig. 1). Therefore, the Bi-PhOH unit mimics the function of the Tyr$_z$-His190 pair of PSII.[6] Irradiation of the Bi–PhOH–PF_{10}–TiO_2 assembly triggers sequential electron transfer and then proton-coupled electron transfer reactions that yield the final charge separated state BiH^+–$PhO^\bullet$–PF_{10}–$TiO_2^{\bullet-}$. This state is characterized by a cationic benzimidazole group, a phenoxyl radical, a neutral porphyrin, and an electron on the semiconducting TiO_2 nanoparticle (Fig. 1).[5a] This final charge separated state is thermodynamically capable of water oxidation, rendering the system an attractive candidate for application in water splitting photoelectrochemical systems.

The preparation of the multi-functionalized porphyrin core of this photosynthetic model presents several substantial synthetic challenges. In the first place, it includes a phenol group, which usually is not compatible with standard porphyrin protocols.[4c] Secondly, the typical synthesis of a benzimidazole

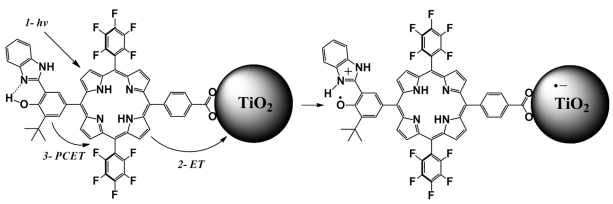

Fig. 1 A molecular triad photosynthetic model composed of three covalently linked redox-active subunits which mimic the photo-redox processes in Photosystem II.

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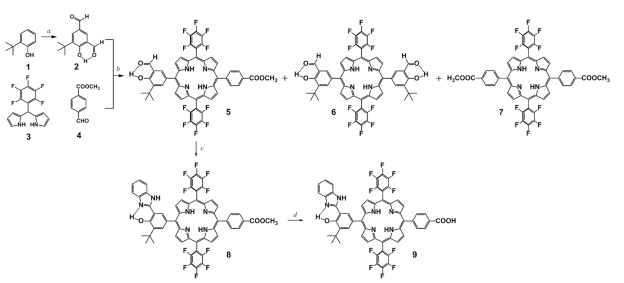
group involves the condensation of *ortho*-phenylenediamine and carbonyl compounds such as formyl, carboxylic acid, or activated esters.[7] This means that the formation of the benzimidazole group at the position required for our purpose demands the preparation of a porphyrin precursor containing a *meso* phenol group bearing one of the "problematic" carbonyl functionalities at its *ortho* position. In addition, perfluorinated porphyrins are known to easily undergo nucleophilic substitution,[8] restricting even further the reaction conditions that might be used to circumvent the synthetic challenges imposed by our design. Fourthly, the carboxylic acid functional group needed for anchoring to the TiO_2 nanoparticle precludes the use of redox reactions to introduce any of the suitable carbonyl functional groups cited above for the formation of the benzimidazole moiety. Finally, the energetics of our photosynthetic model[5a,b] demands a free base porphyrin, which can coordinate transition metal ions. Therefore, transition-metal catalyzed reactions need to be avoided in the synthetic strategy to prevent the coordination of metal ions into the porphyrin core.[9]

Although the use of protecting groups or several additional synthetic steps could solve some of these issues, we decided to pursue a different approach based on contemporary concepts applied to organic synthesis, such as atom economy,[10a] supramolecular assistance to covalent synthesis,[10b] and organocatalysis.[10c] To prepare our photosynthetic model, we envisioned the straightforward synthetic strategy depicted in Scheme 1 which does not involve any re-functionalization or the manipulation of protecting groups. This method is grounded on first preparing the phenol derivative **2**,[11] which bears two formyl functionalities, one at the *para* position for the porphyrin condensation reaction and the other at the *ortho* position for further formation of the benzimidazole component. The key advantage that substantially reduces the number of synthetic steps needed to form the final compound **9** lies in the selective condensation of the formyl group at the *para* position of **2** to yield the porphyrin intermediate **5**. We reasoned that the intramolecular hydrogen bond between the phenolic proton and the *ortho*-formyl residue in **2** would create an asymmetry in the reactivity of the two carbonyl groups towards acid catalyzed condensation reactions. By adjusting the reaction conditions to



Scheme 1 Synthetic strategy based on the use of an intramolecular hydrogen bond to direct the selective acid condensation of formyl groups for the preparation of a multi-functionalized porphyrin photosynthetic model. (*a*) hexamethylene tetraamine, trifluoroacetic acid, reflux, 24 h; (*b*) chloroform, $BF_3{\cdot}OEt_2$, room temperature, 1h, followed by oxidation with DDQ for 12 h at room temperature; (*c*) *ortho*-phenylenediamine, nitrobenzene, reflux, 12 h; (*d*) trifluoroacetic acid/hydrochloric acid (1 : 2, v/v), reflux, 24 h.

favor the formation of this intramolecular hydrogen bond, the carbonyl lone pair of the *ortho*-formyl group would not be available for acid activation, whereas the formyl group at the *para* position would have unencumbered reactivity, resulting in the selective formation of the desired porphyrin **5**.

Noncovalent interactions such as hydrogen bonds are extremely sensitive to their chemical environment.[10b] In order to exploit their full capabilities, optimization of their thermodynamic and kinetic stability is crucial. Usually, this process involves extensive laboratory tests, where parameters such as solvent polarity, concentration, and temperature are scrutinized to determine the most favorable balance for a specific interaction. In the case of **2**, concentration has little influence because the hydrogen bond is formed *via* an intramolecular interaction. However, polar protic solvents and high temperature can potentially promote the disruption of this interaction.[12] Fortunately, the usual conditions for the porphyrin formation (high dilution in a nonpolar aprotic solvent and reaction at room temperature) provide favorable conditions for stabilizing the intramolecular hydrogen bond in **2**. Therefore, the key selectivity needed for the success of the strategy depicted in Scheme 1 would likely be afforded under the conditions of the Lindsey method,[4c] a standard protocol for porphyrin synthesis. Moreover, the bulky *tert*-butyl group at the C-3 position in **2**, originally introduced in our design to prevent dimerization of eventual photo-generated phenoxyl radicals,[13] provides a steric shield against external molecules that might compete for the hydrogen bond, resulting in further stabilization.

To verify this hypothesis, compound **2**, 5-(pentafluorophenyl)-dipyrromethane **3**,[5a] and methyl-4-formylbenzoate **4** were allowed to react under Lindsey conditions.[4c] In a typical experiment, the starting materials were dissolved in freshly distilled chloroform under a nitrogen atmosphere, boron-trifluoride etherate (BF_3OEt_2) was added, and the reaction mixture was stirred for 1 h at room temperature. The resulting dark red porphyrogenic mixture was oxidized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) for 12 h at room temperature, yielding a black crude mixture. Filtration through a silica pad to remove tar and polymeric byproducts followed by concentration under reduced pressure afforded a deep purple-reddish solid. Purification by column chromatography (SiO_2, hexanes/dichloromethane as eluent) yielded three porphyrin fractions (23% total porphyrin yield). The target porphyrin **5** corresponded to the second fraction eluted (11% yield), while the first (7% yield) and third (5% yield) fractions were unambiguously identified as porphyrins **6** and **7** (Scheme 1), respectively. No other porphyrin product was observed in the crude mixture, indicating that the *ortho*-formyl group did not undergo side reactions under the conditions investigated. The exclusive formation of porphyrins **5**, **6**, and **7** from the condensation attests to the efficacy of the intramolecular hydrogen bond for preventing activation of the *ortho*-formyl group in **2** by the BF_3OEt_2 catalyst under proper conditions and demonstrates the successful selectivity of our strategy.

^{1}H NMR analysis in $CDCl_3$ (Fig. 2) provided clear evidence for the selective formation of target porphyrin **5**. The strong downfield shifted peak of the phenolic proton resonance from the usual region (5–6 ppm) to 12.20 ppm gives unmistakable evidence for the presence of the intramolecular hydrogen bond

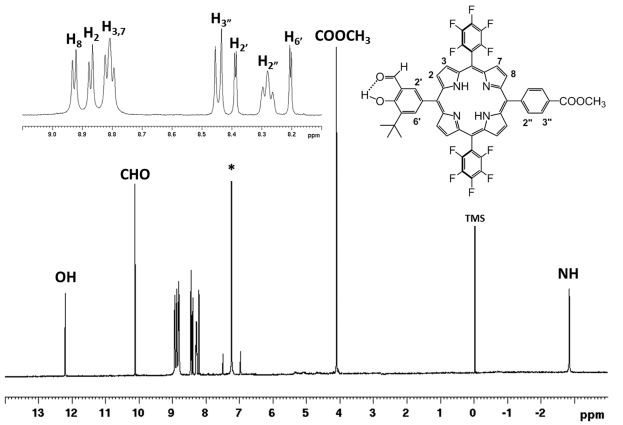


Fig. 2 ^{1}H NMR spectra of porphyrin **5** (400 MHz, $CDCl_3$, 25 °C). The peak marked with an asterisk is due to residual protons in the solvent. TMS = tetramethylsilane.

in **5**. Assignment of this peak to the phenolic group is supported by its absence in the spectrum after addition of a few drops of deuterated methanol to the $CDCl_3$ solution. The formyl proton resonance appears at 10.12 ppm, confirming no side reactions with this group. The porphyrinic core is revealed by the resonance of the pyrrolic protons at 8.93, 8.87, and 8.80 ppm as well as by the peak at −2.75 ppm attributed to the inner NH protons. The two doublets observed at 8.39 and 8.20 ppm are *meta*-coupled (J = 2.0 Hz) and therefore assigned to the protons $H_{2'}$ and $H_{6'}$. The aromatic doublet at 8.45 ppm (J = 8.3 Hz) is coupled to the broad triplet peak at 8.28 ppm and corresponds to $H_{3''}/H_{5''}$ and $H_{2''}/H_{6''}$, respectively. MALDI-TOF spectrometry corroborated the proposed structure for porphyrin **5**, showing an ion peak at (m/z) 952.46 $(M)^+$ (calculated 952.21 for $C_{51}H_{30}F_{10}N_4O_4$).

Compound **5** was successfully converted into **9** through reaction with *ortho*-phenylenediamine in nitrobenzene under reflux to give **8** (ref. 7) followed by acid hydrolysis of the carboxymethyl ester group with a 70% overall yield. Electrochemical investigation of **8** in benzonitrile revealed two (quasi)reversible anodic processes at + 1.28 V and + 1.50 V (*vs.* NHE) which are attributed to the one electron oxidation of the phenol group and the first oxidation of the porphyrin core, respectively. These values indicate that once the artificial photosynthetic model **9** is attached to TiO_2 nanoparticles, the phenoxyl radical (at ∼ 1.3 V *vs.* NHE) should have sufficient driving force for the oxidation of water (0.82 V *vs.* NHE, pH = 7).[5a,b] Furthermore, the presence of an intramolecular hydrogen bond in the benzimidazole-phenol group renders the phenol oxidation process reversible, opening up the possibility of using this system as a redox active relay as part of a photoanode in a water splitting device.

In summary, we report an approach to the synthesis of multi-functionalized porphyrins wherein proper incorporation of noncovalent interactions in the synthetic design induces advantageous selectivity in this complex chemical transformation. The heart of the methodology centers on the fine-tuning of formyl chemical reactivity through formation of a neutral intramolecular O–H—O═C hydrogen bond, which effectively prevents activation of the carbonyl moiety by acid catalysts. The preparation of a multicomponent artificial photosynthetic model that can mimic certain aspects of Photosystem II provides a clear example of the usefulness of this approach. Although we have investigated the effectiveness of this approach only for the O–H—O═C hydrogen bond type, we believe that this methodology can be extended to other hydrogen bond synthons,[12] opening up the possibility of preparing even more complex porphyrins and photosynthetic models. These possibilities are under current investigation.

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