Synthesis of Sterically Encumbered Porphyrins as Catalysts for Shape-Selective Oxidations

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SUMMARY: A general method is described for the synthesis of sterically encumbered porphyrins whose shielding superstructure can take on the enzymatic role of substrate discrimination. This method is based on an improved synthesis of pyrroles substituted with a 2,6-dibromophenyl group, followed by a Suzuki cross-coupling to replace the Br with aryl groups. Porphyrins assembled from such pyrrole units have a barrel shape with the metal center completely fenced by four β-substituted terphenyl shielding wings. The Fe and Mn porphyrins prove to be excellent catalysts for regioselective epoxidation of alkenes.

Introduction

Cytochromes P450 perform intrinsically difficult oxidations often with high regio- and stereoselectivity.[1)] While the use of metalloporphyrins as models for the enzyme is now firmly established, the creation of selective oxidation catalysts is still in an early stage of development.[2)] We aim to study sterically shielded porphyrin catalysts to achieve selective oxidations. Synthetic porphyrins having shielding superstructures are the cornerstone of many important advances that successfully elucidated the heme protein reaction mechanisms. For example, reversible dioxygen binding of hemoglobin and myoglobin have been modeled by a plethora of intriguingly designed porphyrins which invariably incorporate steric barriers to inhibit the formation of the Fe-O-Fe dimer and irreversible oxidation.[3-5)] Likewise, sterically protected metalloporphyrins have shown good activities to catalyze the dioxygenation of organic substrates, thus, mimicking the basic cytochrome P-450 function.[6)] Highly sterically crowded porphyrins, however, are difficult to synthesize, relying on the traditional one-step pyrrole-aldehyde condensation or the multi-step cyclophane-porphyrin synthesis. Recently, we have developed a facile synthesis of double-pocket and barrel-shaped porphyrins, thereby making these coveted molecules much more accessible.[7-9)] Herein, we summarize the synthetic development, structural features, and catalytic applications of these porphyrins.

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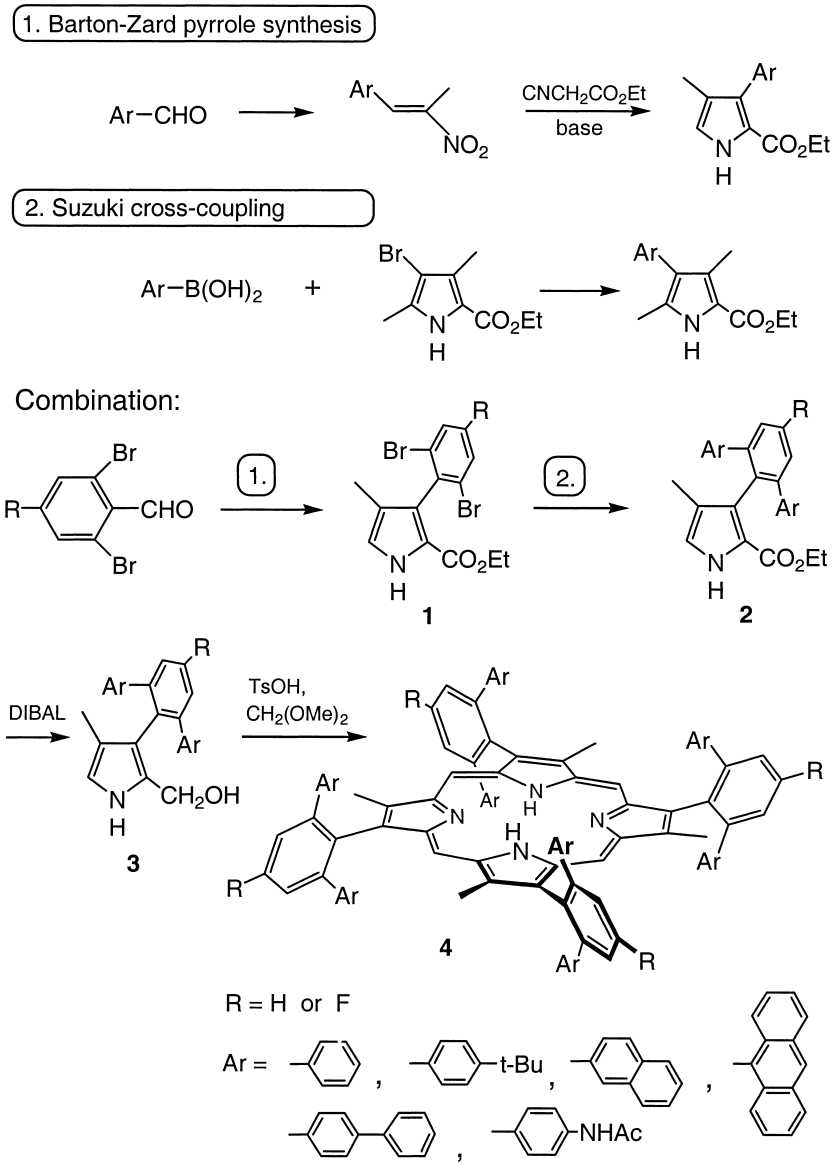
Porphyrin Synthesis

Our synthetic strategy is based on two separate reactions that have shown utility in the pyrrole and porphyrin syntheses. The first is Barton and Zard's discovery[10] of the condensation of nitroalkenes and isocyanaoacetate to yield β-substituted pyrroles which subsequently can be reduced to alcohol and cyclized into porphyrin.[11] We have used this approach to prepare a number of sterically shielded porphyrins having four bulky shielding wings at the β-positions. However, the yield of pyrrole with the Barton-Zard condensation diminishes rapidly with increasing steric hindrance of the aryl group. With a *m*-terphenyl substituent, for example, it is critical to employ a very strong non-nucleophilic base to achieve any pyrrole product.[7] The second reaction is the palladium-catalyzed Suzuki cross-coupling which has been applied in the synthesis of β-phenyl pyrroles and multiple aryl-substituted porphyrins.[12-13] Unfortunately, steric effect again is detrimental to the yield. For example, while 8 molecules of phenylboronic acid can be successfully coupled to octabromo-TPP,[14] it is not possible to couple a sterically hindered *m*-terphenylboronic acid to any bromoporphyrins or bromopyrroles.[15]

The shortcomings of the above two reactions can be circumvented by combining the two in tandem to afford a much more flexible and powerful synthesis. As shown in the Scheme, 2,6-dibromobenzaldehydes are converted to the pyrroles in greater than 80% yields by the Barton-Zard method. A variety of aromatic moieties can then be introduced to the pyrrole nucleus **1** by using the Suzuki cross-coupling, often with > 90% yields. The aryl groups introduced include naphthalenes, biphenyl, and anthracene. By selecting the proper reaction conditions, we have also incorporated many functional groups to the aryl group, e.g. -COOH, -NHAc, -OH, etc. For porphyrin synthesis, pyrrole such as **2** is reduced with DIBAL and cyclized in the presence of an acid catalyst. ^{1}H NMR revealed that the expected type I porphyrin product is obtained without contamination of type II-IV isomers, attesting to the fact that the steric bulk of the aryl group has a major influence in directing the pyrrole cyclization and preventing the scrambling of the substituents even in the acidic medium. Excellent yields of porphyrin **4** (40-65%) have been achieved in the cyclization step, rendering the overall yield from the aldehyde in the range of 25-45%. This is quite a contrast to the 1% best-case yield of a *meso*-substituted bis-pocket porphyrin first reported by Suslick,[16] which cannot be improved by the Lindsey's method.[17]



Scheme. Synthesis of shielded porphyrins

Porphyrins **4** have been thoroughly characterized by NMR, mass spectra, and X-ray structural analyses. The X-ray structures confirmed that the four aromatic moieties are nearly perpendicular to the porphyrin plane, thus projecting the two ortho-aryl groups above and below like two giant wings to cover the porphyrin center. Because the

shielding wings are attached at the β-positions, there is a certain degree of mobility associated with these wings. The smallest terphenyl wings have a tendency to rotate toward the porphyrin ring, with an average angle of 62.4° between the terphenyl and the macrocycle planes. The rotational freedom is much reduced when the aryl wings are substituted and become bigger. The acetanilido group is designed with a specific purpose: the hydrogen-bonding interactions occurring among the amide groups interlock the wings and thereby tightening the pocket, much like fastening a bag with a string.

The Fe(II) complex of these bis-pocket porphyrins, as expected, can reversibly bind dioxygen at room temperature, in solution, with extremely good stability. In the presence of 1,2-dimethylimidazole (0.3 M) in toluene, the half-saturation pressure $P_{1/2}$ is 467 torr for the terphenyl-winged porphyrin. The rather poor oxygen affinity is a result of the nonpolar nature of the O_2-binding pocket. The O_2 affinity displays a dependence on the solvation effect; the detailed study is published elsewhere.[8)]

Regiospecific epoxidation

The aromatic shielding wings of this series of porphyrins create a tunnel-like channel on both faces of the porphyrin, which can be exploited effectively to mediate shape and regioselective oxidations. Previously, Suslick has used the meso-substituted bis-pocket porphyrin to demonstrate shape-selective epoxidation and hydroxylation of the sterically most accessible site(s).[2)] Similarly, "picnic basket" porphyrins and dendrimer-porphyrins with varying pocket size also show selectivity in epoxidizing olefins.[18-19)] Generally, there are two types of tests for selectivity: intramolecular competition between two sites in a molecule, or intermolecular competition between two contrasting molecules. In our study, we have used both approaches to examine the effectiveness of the new porphyrins in catalyzing regioselective epoxidation. We chose to use Mn(III)Cl porphyrin complexes as catalyst (Fe complexes also work well). Reactions were carried out at 23°C in CH_2Cl_2 with 1 mM of alkene, 0.002 mM of catalyst, and 0.05 mM of iodosylbenzene (as oxygen donor), and the products were analyzed by GC after 1 h of reaction.

The result for the intermolecular selectivity between two alkenes is shown in Fig. 1. A 1:1 mixture of 1-hexene and *cis*-cyclooctene was employed to probe the steric differentiation. Normally, the electron rich *cis*-cyclooctene is preferentially attacked. For example, with unhindered Mn(III)TPP·Cl as control, the yield of 1-hexene oxide is less than 1% of the total epoxide products. However, for the barrel-shaped catalysts, more preferential attack

can occur at the terminal double bond relative to the less accessible *cis*-cyclooctene. Indeed, the results shown in Fig. 1 make it quite clear that the selectivity is inversely dependent on the accessibility to the reactive metal center and/or on the size of the cavity.

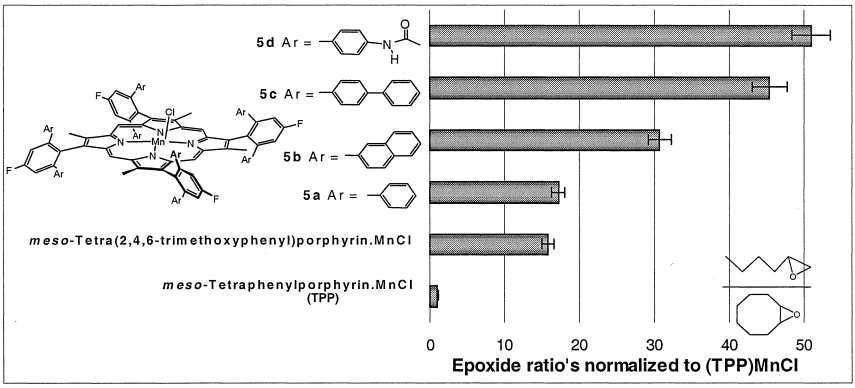


Figure 1: Selective epoxidation revealed by using a mixture of 1-hexene and *cis*-cyclooctene. The epoxide ratio's were normalized to the unhindered MnCl(TPP).

Results for intermolecular selectivity have been obtained by studying the epoxidation of a series of non-conjugated dienes and comparing the relative reactivity of the terminal versus the more sterically crowded internal double bonds. These results are summarized in Fig. 2 which include also the data of *m*-chloroperbenzoic acid (mcpba). Again, the new catalysts (**5a –5d**) demonstrate superior selectivity toward the terminal alkene when compared with the previous benchmark - the meso-substituted bis-pocket porphyrin.[2, 20)]

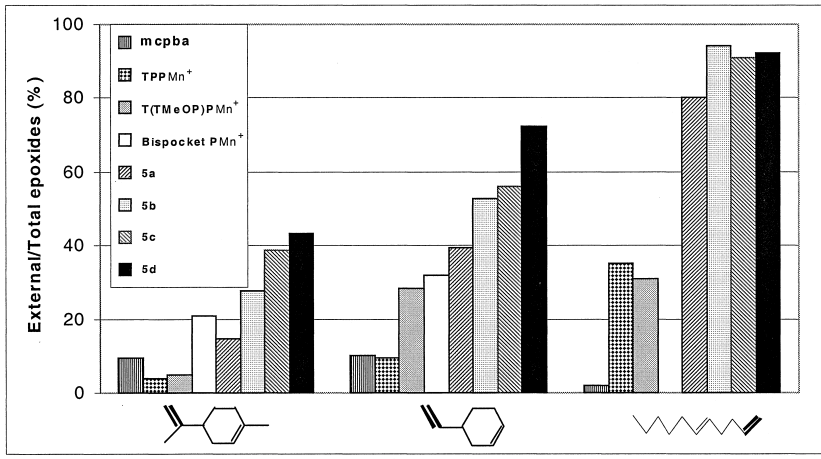


Figure 2: Percentage of epoxidation at the terminal double bond (bold).

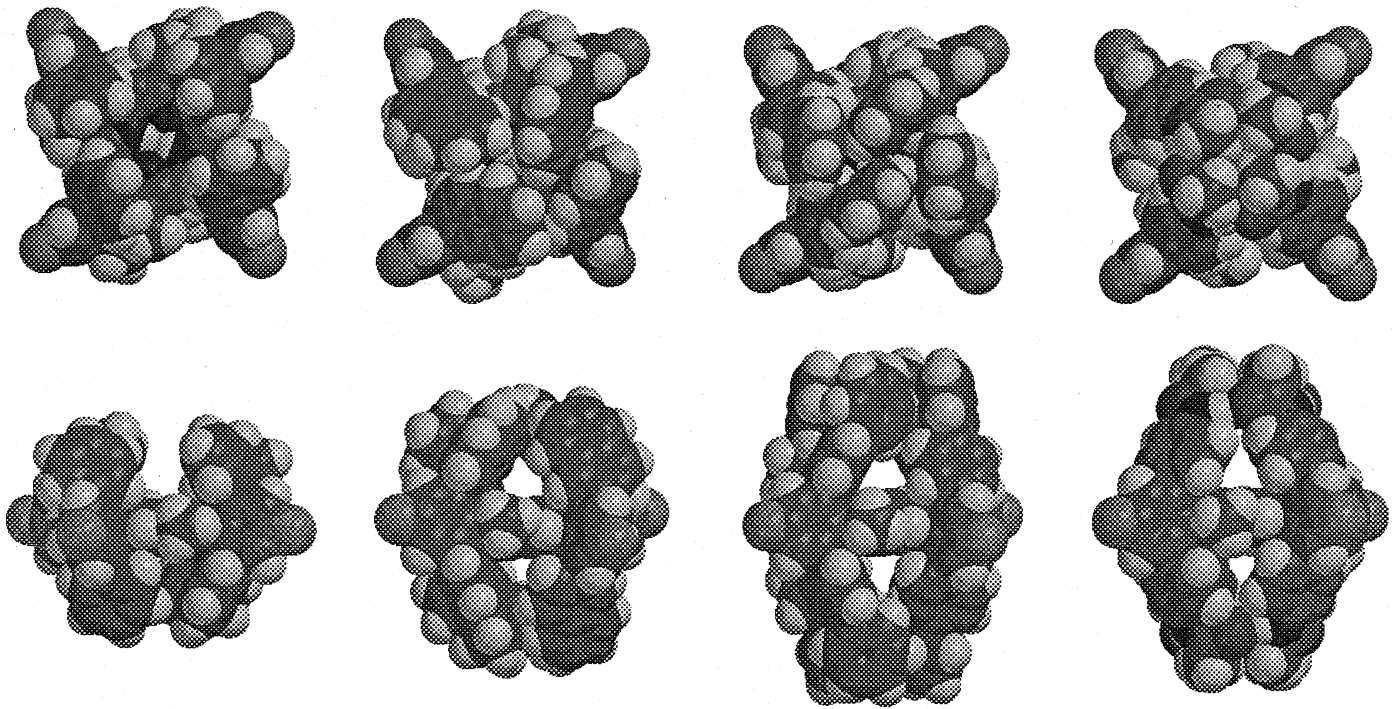


Figure 3: Molecule models of the porphyrins, top view (upper) and side view (lower). (A) Ar = phenyl, smallest of the series, cavity permits free access to the porphyrin center. (B) Ar = 2-naphthyl, the top opening is blocked by the naphthyl wings. (C) Ar = *p*-biphenyl, the top is blocked but the pocket is elongated. (D) Ar = *p*-acetanilide. The H-bonds produce a better alignment of the wings and zip up the opening.

In the above tests, the selectivity increases with the size of the shielding wings. The highest selectivity is shown by the *p*-acetamido **5d**. X-ray structures and molecular modeling help us understand the structure-activity relationship. Fig. 3 provides the top and side views of the four porphyrin catalysts. For the smallest terphenyl porphyrin (**A**), the open cavity at the top is roughly 0.5 nm and a similar sized gap can be seen on the side between the wings. Such openings should allow a relative easy access to the active metal center. The top opening is essentially closed in the 2-naphthyl- and *p*-biphenyl-winged porphyrins (**B** and **C**), but there are numerous alternative conformations readily achievable to open up the pocket. The mobility in the superstructure permits the catalytic reactions to proceed with a variety of substrates. In porphyrin **D**, the intramolecular hydrogen bonds among the amide groups not only lock the phenyl groups in an upright position, but also limit their free rotations. It is not surprising that the highest inter- and intramolecular selectivities have been achieved with **5d**. Molecular modeling suggests that in this case the reactants likely enter the pocket sideways through the gap. Due to the steric constraints, the reaction rate for **5d** is also significantly slower than the other catalysts. Turnover rates observed for these highly shielded porphyrins are in the range of 1 to 3 sec^{-1} and are somewhat slower than Mn(III)TPP (3-4 sec^{-1}).

Metalloporphyrins have a marked proclivity for self-destruction in oxidizing environment. In general, destructive oxidation occurs at the *meso*-carbon. The oxidative stability of metalloporphyrins can be increased by introducing sterically bulky substituents at he meso-positions. The system we studied here bears no substituent at the *meso*-positions. Nevertheless, our porphyrins exhibit high oxidative stability comparable to that of the fully meso-substituted bis-pocket porphyrin. Thus, the steric protection afforded by the β-wings is sufficient to prevent the meso-carbon being attacked by the reactive metal-oxo species leading ultimately to the porphyrin ring cleavage.

Conclusion

Highly sterically hindered porphyrins can be synthesized from 2,6-dibromobenzaldehydes. Our method takes advantage of two relatively recent yet increasingly popular reactions, and by running these two reactions in tandem, we have found a powerful and flexible way to tackle an old problem, i.e. how to prepare sterically protected porphyrins easily and with good yield. The new porphyrins have been examined as shape-selective oxidation catalysts. Their Mn(III) complexes show very high selectivity

for epoxidation of dienes and linear alkenes. The high selectivity is attributed to the increasing steric crowding of the pocket created by the shielding superstructure.

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