A 'Click' Chemistry Route to 'Capped' Porphyrins

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Received 23 March 2008

Dedicated to Professor Sir Jack Baldwin FRS on the occasion of his 70th birthday in appreciation for teaching one of us how to think at a deeper level about molecules and what is happening on the molecular scale

Abstract: Synthesis of a new 'capped' porphyrin **3** with rigid 1,2,3-triazole linkers between the porphyrin and 'capping' group has been achieved. A 'click' reaction, the copper(I)-catalysed variant of the Huisgen 1,3-dipolar cycloaddition, is used to create four linkages concomitantly under anhydrous conditions in N,N-dimethylformamide.

Key words: porphyrin, alkyne, azide, 1,3-dipolar cycloaddition, 1,2,3-triazoles

Baldwin's 'capped' porphyrin 1 represents a landmark in design and synthesis of functional molecules and established the paradigm for 'molecular engineering'.¹ The 'capped' porphyrin has great beauty and its iron chelate mimics aspects of the oxygen-carrying function of myoglobin.² A particularly elegant example from the Baldwin group is the more elaborated 'strapped' 'capped' porphyrin **2** (Figure 1).³ These synthetic mimics revealed insights not easily discerned by study of natural systems; for example, the means by which carbon monoxide binding can be reduced.² These studies focused attention on the diverse and complex porphyrin-containing structures found in nature like the light-harvesting complexes I and II, haemoglobin, myoglobin, and proteins such as cytochrome C and F_{430} .

Baldwin's 'capped' porphyrin **1** was synthesised by two synthetic paths, one utilising one-step Adler–Longo⁴ condensation of a tetraaldehyde and pyrrole under high dilu-

tion conditions (2–28% yield), and the other involving reaction of an isomeric mixture of the corresponding porphyrin tetraalcohol with pyromellitic tetraacid chloride (15% yield).¹ The convergent synthesis of **1** involved the separation of various atropisomers,¹ a consequence of the restricted rotation of *ortho* substituted *meso*-aryl groups.⁵

Superstructures of 'capped' porphyrins provide a cavity within which the selective binding of small molecules to the chelated metal ion can occur. This is of great interest given the potential of the metal centre to be catalytically active. A measure of cavity size is the separation between the centroid of the capping aryl group and the porphyrin macrocycle. This distance is 3.96 Å in the crystal structure of 1.⁶ Interestingly, the 'C₃-capped' porphyrin, homologous to 1 but with an extra methylene group in each linking rib, has a smaller cavity. Intuitively the extra methylenes would be expected to lead to a larger cavity than 1. The crystal structure, however, showed the separation of cap and porphyrin planes is only 3.49 Å,⁷ a result of the ribs being less rigidifying.

We now report the synthesis of 'capped' porphyrin **3** through convergent regioselective Cu(I)-catalysed cycloaddition of an azide and an alkyne 'click' chemistry,⁸ forming rigid 1,2,3-triazoles as linkers in the 'capped' porphyrin (Scheme 1). A key consideration was the need to construct a 'capped' porphyrin with a cavity that will not collapse onto the macrocycle.



Figure 1 Baldwin's 'capped' porphyrin 1 and 'strapped' 'capped' porphyrin 2

SYNLETT 2008, No. 14, pp 2147–2149 Advanced online publication: 02.07.2008 DOI: 10.1055/s-2008-1077899; Art ID: D10208ST © Georg Thieme Verlag Stuttgart · New York



Scheme 1 Reagents and conditions: Method A: 10% H_2O in THF, $CuSO_4 \cdot 5H_2O$, L-ascorbic acid, Et_3N . Method B: DMF, $Cu(MeCN)_4PF_6$, Et_3N .

Capping group precursor **4** was obtained in 74% yield by reaction of propargyl alcohol with pyromellitic tetraacid chloride in the presence of triethylamine.⁹ Tetraazide porphyrin **5** was obtained from [5,10,15,20-tetrakis-(3-bromomethylphenyl)porphyrinato]zinc(II) in 86% yield by treatment with NaN₃ in DMF; the tetrabromoporphyrin being obtained in 22% overall yield by Rothemund condensation of 3-(bromomethyl)benzaldehyde and pyrrole, followed by metalation using Zn(OAc)₂.

'Capped' porphyrin **3** was formed in moderate yields through the reaction of tetraalkyne **4** with tetraazide **5** (Scheme 1). Two sets of conditions were explored.

Method A^{10} (Scheme 1) used standard conditions of catalytic copper(II) sulfate with L-ascorbic acid in H₂O–THF (1:10) with four equivalents of triethylamine. The presence of a tertiary amine base has been previously shown¹¹ to increase the rate of Cu(I)-catalysed cycloaddition reactions. The reaction was heated at reflux for 30 hours and chromatography of the product over silica, to remove polymeric byproducts, gave the capped porphyrin **3** in 19% yield.¹²

The coupling was also carried out under anhydrous conditions (Scheme 1, Method B) using anhydrous DMF as solvent in conjunction with four equivalents of triethylamine and catalytic copper(I) tetrakis(acetonitrile) hexafluorophosphate. The use of a copper(I) salt avoids the dependence upon a solvent system in which L-ascorbic acid is necessary to reduce the copper(II) species. The reaction was stirred at 70 °C for 16 hours, affording the 'capped' porphyrin **3** in 14% yield.¹³

An interesting point is the deshielding effect of the magnetic anisotropy of the porphyrin ring on the aryl protons of the capping group. In CDCl₃ the resonance of the capping aryl protons of 'capped' porphyrin **1** is shifted upfield to $\delta = 5.49$ ppm, a shift of about 2.7 ppm compared with the precursor tetraaldehyde. This upfield shift, according to the multipole-expansion porphyrin ring current model of Cross and Crossley,¹⁴ corresponds to a time-averaged separation of about 4.2 Å between the centroids of the capping aryl and the 24-atom porphyrin skeleton. In

CDCl₃ the capping aryl protons of 'capped' porphyrin 3 resonate at δ = 7.32 ppm, an upfield shift of 0.83 ppm compared with the resonance of the corresponding protons in 4. Both the Cross and Crossley¹⁴ ring current model and low-level UFF molecular modelling agree on a distance of about 7.2 ± 0.3 Å between the aromatic plane of the capping group and that of the porphyrin in 3. A COESY experiment showed that the *meso*-aryl H2 protons are shifted upfield by 1.33 ppm, compared with the H6 protons, consistent with them falling within the deshielding zone of the 1,2,3-triazoles requiring that the triazoles be orthogonally aligned to the meso-aryls, a conformation supported by the modelling. The relatively large cavity that is formed can be attributed to the rigid triazole linkers preventing collapse of the capping group onto the porphyrin.

In summary, we have applied 'click' chemistry to attach a capping superstructure to a porphyrin. The concomitant formation of four linkages between a porphyrin-tetraazide and an arene-tetraalkyne was achieved in both hydrous and anhydrous conditions, with similar yields. This methodology allows the incorporation of a number of sensitive functional groups and highlights the ease in which sophisticated molecular architectures can be generated utilising 'click' chemistry in conjunction with a porphyrin substructure.

Acknowledgment

We thank the Australian Research Council for funding for this research.

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LETTER

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- (9) Selected data for compound 4: mp 119–120 °C. ¹H NMR (200 MHz, CDCl₃): δ = 8.15 (s, 2 H), 4.95 (d, *J* = 2.45 Hz, 8 H), 2.57 (t, *J* = 2.45 Hz, 4 H). ¹³C NMR (75 MHz, CDCl₃): δ = 164.9, 133.9, 130.1, 76.7, 76.0, 53.8.
- (10) **Tetrahydrofuran–H₂O Method for the Cycloaddition**: To a stirred mixture of porphyrin **5** (65 mg) and Et₃N (40 μ L) in THF (100 mL) were added CuSO₄·5H₂O (4 mg) and ascorbic acid (5 mg) dissolved in H₂O (15 mL). Then a solution of tetraalkyne **4** in THF (35 mL) was added and the mixture was heated at reflux for 24 h. An additional portion of CuSO₄·5H₂O (4 mg) and L-ascorbic acid (5 mg) in H₂O (5 mL) was added and refluxed for a further 6 h. The reaction was then filtered, evaporated to approximately 20 mL with CH₂Cl₂ (100 mL) and H₂O (100 mL) added. The organic

phase was collected and the aqueous phase was extracted with a mixture of MeOH and H_2O (1:1, 2 × 100 mL). This was then dried over Na₂SO₄, filtered and evaporated. Purification on silica with 4% MeOH in H₂O yielded capped porphyrin **3** in 19% yield.

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- (12) Selected data for compound 3: mp >300 °C. ¹H NMR (400 MHz, CDCl₃): δ = 8.72 (s, 4 H), 8.68 (s, 4 H), 8.41 (br d, J = 7.6 Hz, 4 H, meso-aryl H6), 7.85 (t, J = 7.6 Hz, 4 H, meso-aryl H3), 7.77 (br d, J = 7.6 Hz, 4 H, meso-aryl H4), 7.64 (br s, 4 H), 7.32 (s, 2 H), 7.08 (br s, 4 H, meso-aryl H2), 5.93 (A of ABq, J = 16.1 Hz, 4 H), 5.79 (B of ABq, J = 16.1 Hz, 4 H), 5.13 (A of ABq, J = 13.0 Hz, 4 H), 5.03 (B of ABq, J = 13.0 Hz, 4 H). MS (ESI): m/z [M + Na] calcd for C₇₀H₄₆N₁₆O₈Zn: 1325.3; found: 1325.4.
- (13) **Dimethylformamide Method for the Cycloaddition**: To a stirred solution of **5** (45 mg), (NCCH₃)₄CuPF₆ (4 mg) and Et₃N (28 μ L) in DMF (100 mL) was added **4** (20 mg). This was then put under nitrogen and stirred at 70 °C for 16 h. This was then added to a mixture of CH₂Cl₂ and EtOAc (1:1, 200 mL), washed with H₂O (2 × 100 mL), and the organic phase was filtered and washed again with H₂O (2 × 100 mL). The organic phase was then dried over Na₂SO₄, filtered and evaporated with the residue subjected to purification on silica, eluting capped porphyrin **3** in 14% yield.
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