Synthesis of New Strapped Porphyrins via a Bisdipyrromethane Condensation

Diana P. N. Gonçalves, Jeremy K. M. Sanders*

University Chemical Laboratory, Cambridge University, Lensfield Road, Cambridge, CB2 1EW, UK
Fax +44(1223)336017; E-mail: jkms@cam.ac.uk

Received 25 October 2006

Abstract: Two new cationic strapped *meso*-porphyrins were synthesized via a new route, which consists of the condensation of a bisdipyrromethane with an aldehyde under acidic conditions. One of the strapped porphyrins binds to G-quadruplex DNA.

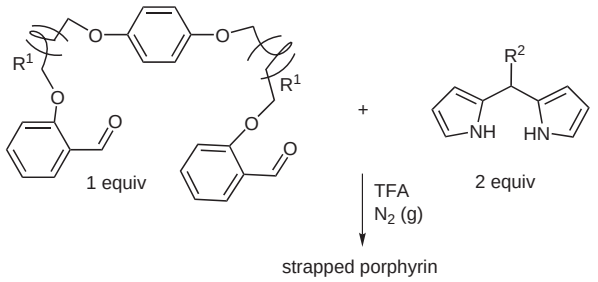
Key words: strapped porphyrins, condensation, synthesis, *meso*, bisdipyrromethane

In the past century there have been many reports of strapped porphyrins in the literature. They presented different structural features for a wide range of applications; including disulfide-containing strapped porphyrins for gold surface interactions,[1] models for oxidized states of cytochrome c oxidase,[2] building blocks for catenane synthesis;[3] just to name some of the many examples.[4]

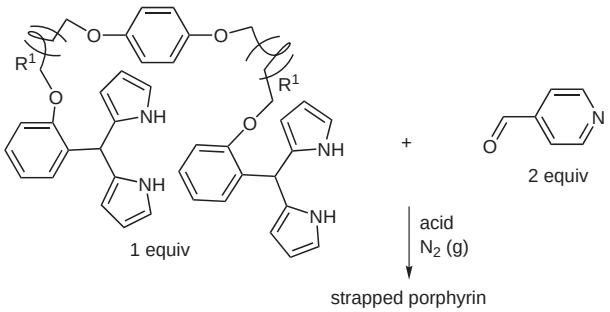
Herein, we report the synthesis of two new cationic *meso*-substituted porphyrins with different strap sizes (Figure 1) by a new synthetic method.

The standard synthesis of strapped *meso*-porphyrins consists of the condensation of a dialdehyde with a dipyrromethane (Scheme 1).[2–5]

In our new synthetic route a bisdipyrromethane is reacted with an aldehyde (Scheme 2). A related approach for the synthesis of β-pyrrole-strapped porphyrins has been previously reported by Wijesekera et al.[6]



Scheme 1



Scheme 2

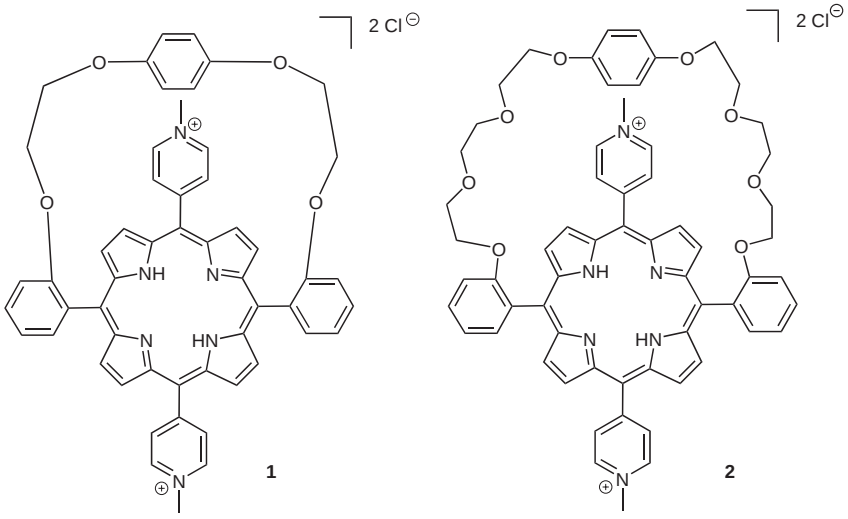
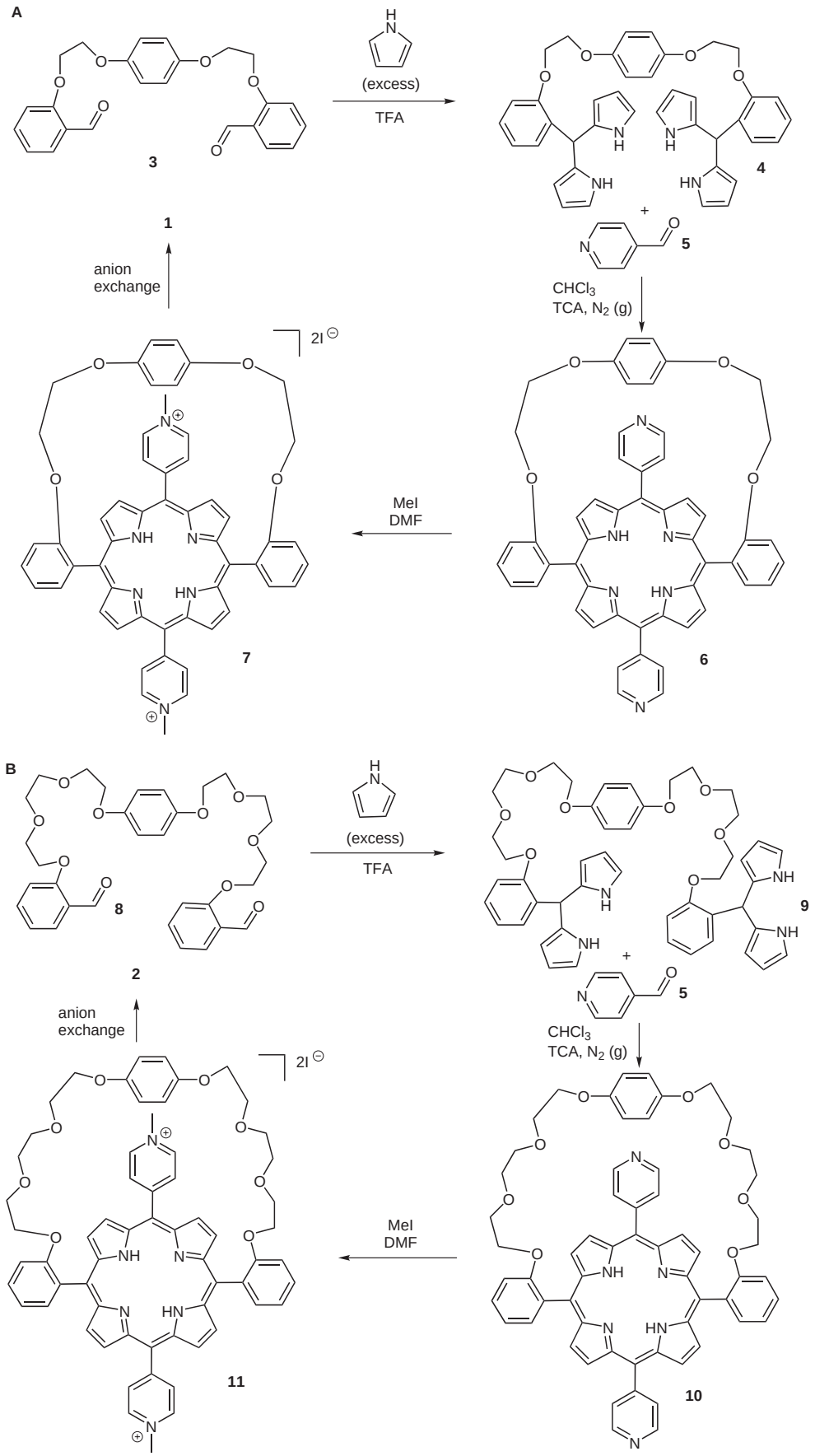


Figure 1

SYNLETT 2007, No. 4, pp 0591–0594
Advanced online publication: 21.02.2007
DOI: 10.1055/s-2007-967967; Art ID: D31506ST



Scheme 3 Stepwise synthesis of strapped porphyrins **1** (pathway **A**) and **2** (pathway **B**), via a new synthetic route

The synthesis of bisdipyrromethanes **4** and **9** was achieved in quantitative yields by reacting a large excess of pyrrole with dialdehydes **3** or **8** in the presence of 1.4 equivalents of TFA, for 15 minutes at room temperature (Scheme 3).[7] The synthesis of dialdehydes **3** and **8** has been previously reported elsewhere and is suitable for scale-up.[3,5] The condensation of bisdipyrromethanes **4** or **9** with 2 equivalents of aldehyde **5** in the presence of 13 equivalents of trichloroacetic acid (TCA) and under nitrogen yielded 0.9% and 19% of porphyrins **6** and **10**, respectively, after chromatographic purification.[8] The conventional synthetic pathway exemplified by Scheme 1 yielded 2–4% of porphyrin **10** and a very small amount of non-quantified residue of porphyrin **6**.

This new synthetic route appears to be more efficient with bisdipyrromethane **9** due to its larger ethylene glycol chain and flexibility, contrasting with the smaller and more sterically hindered bisdipyrromethane **4**.

Quaternization of porphyrins **6** and **10** with iodomethane in DMF yielded quantitatively porphyrins **7** and **11**.[9] The final porphyrins **1** and **2** were obtained quantitatively after submitting porphyrins **7** and **11** to anion exchange, where the iodide counter anion was replaced by a chloride.[10]

In order to explore the use of bisdipyrromethanes as a general route to synthesize strapped porphyrins, bisdipyrromethane **9** was reacted with other aldehydes (benzaldehyde, tetrafluorobenzaldehyde, 4-methylbenzaldehyde and 4-nitrobenzaldehyde), but without success. We are currently investigating this reaction in more detail.

The porphyrin with the longest strap (**2**) binds to G-quadruplex DNA ($k_D = 18 \pm 4$ μM), showing some preference for the antiparallel quadruplex conformation (data not shown).

In summary, a new synthetic route for the preparation of two new cationic-strapped *meso*-porphyrins has been developed. This new method appears to be specific for the condensation with 4-pyridinecarboxaldehyde. Porphyrin **2** has been shown to bind to G-quadruplex DNA.

Acknowledgment

We thank Duncan Howe, Andrew Mason and Brian Crysell for NMR assistance. The Portuguese Science Foundation (Fundação para a Ciência e a Tecnologia – FCT – Portugal) SFRH/BD/12414/2003 (D. P. N. Gonçalves) is gratefully acknowledged for financial support.

References and Notes

(1) Redman, J. E.; Sanders, J. K. M. *Org. Lett.* **2000**, *2*, 4141.
(2) Andrioletti, B.; Ricard, D.; Boitrel, B. *New J. Chem.* **1999**, *23*, 1143.
(3) Gunter, M. J.; Hockless, D. C. R.; Johnston, M. R.; Skelton, B. W. *J. Am. Chem. Soc.* **1994**, *116*, 4810.
(4) (a) Osuka, A.; Kobayashi, F.; Nagata, T.; Maruyama, K. *Chem. Lett.* **1990**, *2*, 287. (b) Osuka, A.; Nagata, T.; Maruyama, K. *Chem. Lett.* **1991**, *10*, 1687.
(5) (a) Ikeda, T.; Asakawa, M.; Miyake, K.; Shimizu, T. *Chem. Lett.* **2004**, *33*, 1418. (b) Anelli, P. L.; Ashton, P. R.; Ballardini, R.; Balzani, V.; Delgado, M.; Gandolfi, M. T.; Goodnow, T. T.; Kaifer, A. E.; Philp, D.; Pietraszkiewicz, M.; Prodi, L.; Reddington, M. V.; Slawin, A. M. Z.; Spencer, N.; Stoddart, J. F.; Vicent, C.; Williams, D. J. *J. Am. Chem. Soc.* **1992**, *114*, 193.
(6) Wijesekera, T. P.; Paine, J. B. III; Dolphin, D. *J. Org. Chem.* **1988**, *53*, 1354.
(7) **Preparation of Compound 4.**
To a flask containing **3** (1.5 g, 3.69 mmol) and pyrrole (118 g, 1.65 mol) was added 1.4 equiv of TFA and the flask was left to stir in open air for 15 min. The reaction was quenched with TEA (7.22 g, 71.4 mmol) and then the unreacted pyrrole was evaporated. The resulting brown oil was purified by column chromatography on silica gel ($CHCl_3$–MeOH, 10:1), yielding **4** quantitatively as a light brown oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.49 (br s, 4 H), 7.21–7.24 (m, 4 H), 6.95–6.92 (m, 2 H), 6.91–6.89 (m, 2 H), 6.87 (s, 4 H), 6.58–6.60 (m, 4 H), 6.06–6.09 (m, 4 H), 5.89–5.90 (m, 4 H), 5.61 (s, 2 H), 4.21–4.23 (m, 4 H), 4.03–4.05 (m, 4 H) ppm. ^{13}C NMR (500 MHz cryo, $CDCl_3$): δ = 155.8, 153.1, 145.7, 132.5, 130.2, 128.2, 121.6, 116.8, 116.6, 112.5, 108.0, 106.4, 67.4, 66.8, 40.4 ppm. HRMS: *m/z* calcd 639.2971; found: 639.2943 [M + H$^+$].
Preparation of Compound 9.
To a flask containing **8** (2.4 g, 4.12 mmol) and pyrrole (236 g, 3.30 mol) was added 1.4 equiv of TFA and the flask was left to stir in open air for 15 min. The reaction was quenched with TEA (7.22 g, 71.4 mmol) and then the unreacted pyrrole was evaporated. The resulting brown oil was purified by column chromatography on silica gel ($CHCl_3$–MeOH, 10:1), yielding **9** quantitatively as a light green oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.24 (dd, *J* = 1.6, 7.6 Hz, 2 H), 7.18 (dt, *J* = 1.6, 7.6, 8.0 Hz, 2 H), 6.91 (dt, *J* = 0.9, 7.6, 7.6 Hz, 2 H), 6.83 (dd, *J* = 0.9, 8.0 Hz, 2 H), 6.76 (s, 4 H), 6.62–6.65 (m, 4 H), 6.08–6.10 (m, 4 H), 5.93–5.94 (m, 4 H), 5.66 (s, 2 H), 4.04–4.06 (m, 4 H), 3.94–3.96 (m, 4 H), 3.77–3.79 (m, 4 H), 3.75–3.76 (m, 4 H), 3.70–3.72 (m, 4 H), 3.65–3.67 (m, 4 H) ppm. ^{13}C NMR (500 MHz cryo, $CDCl_3$): δ = 155.8, 152.9, 132.6, 132.0, 130.1, 128.0, 121.4, 116.5, 115.5, 112.4, 107.8, 106.2, 70.8, 70.7, 69.9, 69.7, 67.8, 67.1, 40.5 ppm. HRMS: *m/z* calcd: 815.3942; found: 815.4121 [M + H$^+$].
(8) **Preparation of Porphyrin 6.**
To a stirred solution of **4** (0.50 g, 1.03 mmol) and 4-pyridinecarboxaldehyde (0.22 g, 2.06 mmol) in CH_2Cl_2 (500 mL), under nitrogen at r.t. and in the dark, was added TCA (2.20 g, 13.46 mmol) dissolved in CH_2Cl_2 (10 mL). After reacting for 90 min, TEA (7.22 g, 71.4 mmol) was added followed by DDQ (0.15 g, 0.66 mmol) and the reaction was stirred for an additional 30 min. The solvent was then evaporated in vacuo and purified by preparative TLC (CH_2Cl_2–MeOH, 10:1), yielding 0.9% of porphyrin **6** (7.5 mg) as a purple solid. UV/Vis: λ_{max} = 418, 518, 556, 602 nm. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.97 (br s, 4 H), 8.86 (d, *J* = 4.8 Hz, 4 H), 8.74 (d, *J* = 4.8 Hz, 4 H), 7.95 (br s, 4 H), 7.83–7.85 (m, 2 H), 7.77–7.81 (m, 2 H), 7.50–7.55 (m, 2 H), 7.20–7.25 (m, 2 H), 3.87–3.85 (m, 4 H), 3.55 (s, 4 H), 2.82–2.84 (m, 4 H), –2.74 (br s, 2 H) ppm. ^{13}C NMR (500 MHz cryo, $CDCl_3$): δ = 159.4, 152.3, 148.2, 134.1, 131.8, 130.2, 129.6, 120.4, 113.4, 69.3, 68.6, 58.6 ppm. As is usual in porphyrin chemistry, many of the quaternary carbon NMR signals are too weak to be seen. HRMS: *m/z* calcd: 811.3033; found: 811.3044 [M + H$^+$].
Preparation of Porphyrin 10.
To a stirred solution of **9** (0.59 g, 0.60 mmol) and 4-pyridinecarboxaldehyde (0.13 g, 1.20 mmol) in CH_2Cl_2

(500 mL), under nitrogen at r.t. and in the dark, was added TCA (2.20 g, 13.46 mmol) dissolved in CH_2Cl_2 (10 mL). After reacting for 90 min, TEA (7.22 g, 71.4 mmol) was added followed by DDQ (0.30 g, 1.32 mmol) and the reaction was stirred for an additional 30 min. The solvent was then evaporated in vacuo and purified by preparative TLC (CH_2Cl_2–MeOH, 10:1), yielding 19% of porphyrin **10** (92.4 mg) as a purple solid. UV/Vis: λ_{max} = 414, 510, 546, 592 nm. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.00 (br s, 4 H), 8.83 (d, *J* = 4.6 Hz, 4 H), 8.74 (d, *J* = 4.6 Hz, 4 H), 8.13 (br d, 4 H), 7.86 (dd, *J* = 1.1, 7.9 Hz, 2 H), 7.76 (td, *J* = 1.6, 7.6, 7.9 Hz, 2 H), 7.43 (d, *J* = 7.8 Hz, 2 H), 7.38 (td, *J* = 1.1, 7.8, 7.6 Hz, 2 H), 5.79 (s, 4 H), 4.06 (t, *J* = 5.2 Hz, 4 H), 3.19 (t, *J* = 5.2 Hz, 4 H), 2.88–2.90 (m, 4 H), 2.83–2.84 (m, 4 H), 2.79–2.81 (m, 4 H), 2.74–2.77 (m, 4 H) and –2.79 (br s, 2 H) ppm. ^{13}C NMR (500 MHz cryo, $CDCl_3$): δ = 158.4, 152.1, 148.1, 136.1, 130.8, 130.1, 129.3, 119.9, 117.2, 116.5, 115.2, 112.7, 70.2, 70.1, 69.0, 68.6, 67.4 ppm. HRMS: *m/z* calcd: 987.4081; found: 987.4041 [M + H$^+$].

(9) **Preparation of Porphyrin 7.**
The quaternization of the pyridyl groups of porphyrin **6** was achieved by methylation with a large excess of MeI in DMF, at 40 °C for 5 h, yielding quantitatively porphyrin **7**.
Preparation of Porphyrin 11.
The quaternization of the pyridyl groups of porphyrin **10** was achieved by methylation with a large excess of MeI in DMF, at 40 °C for 5 h, yielding quantitatively porphyrin **11**.

(10) **Preparation of Porphyrin 1.**
Porphyrin **7** was then submitted to an anion-exchange resin with Dowex 1X2-200 in the chloride form, by shaking the dissolved porphyrin in a mixture of acetone–H_2O (3:2) with the exchange resin for approximately 3 h. The resin was then filtered off and washed with H_2O, giving porphyrin **1** in quantitative yields and without any further purification. UV/vis λ_{max} = 424, 518, 556, 602 nm. ^{1}H NMR (500 MHz, CD_3CN 80% CD_3OD 20%): δ = 9.06 (d, *J* = 5.3 Hz, 4 H), 9.02–8.72 (br m, 12 H), 8.51 (dd, *J* = 1.4, 7.1 Hz, 2 H), 8.88–8.92 (m, 2 H), 7.59 (t, *J* = 7.1, 8.0 Hz, 2 H), 7.37 (d, *J* = 8.0 Hz, 2 H), 4.64 (s, 6 H), 3.89–3.91 (m, 4 H), 3.64 (s, 4 H), 2.91–2.90 (m, 4 H) ppm. The NH signals are not present due to exchange with the solvent. ^{13}C NMR (500 MHz cryo, CD_3CN 80% CD_3OD 20%): δ = 159.5, 153.2, 144.9, 134.8, 131.9, 121.3, 115.9, 114.4, 69.8, 69.2, 49.2 ppm. HRMS: *m/z* calcd: 420.1706 [(M – 2 Cl)/2]; found: 420.1709.
Preparation of Porphyrin 2.
Porphyrin **11** was then submitted to an anion-exchange resin with Dowex 1X2-200 in the chloride form, by shaking the dissolved porphyrin in a mixture of acetone–H_2O (3:2) with the exchange resin for approximately 3 h. The resin was then filtered off and washed with H_2O, giving porphyrin **2** in quantitative yields and without any further purification. UV/vis λ_{max} = 426, 510, 546, 592 nm. ^{1}H NMR (500 MHz, CD_3NO_2): δ = 9.19 (d, *J* = 6.7 Hz, 4 H), 9.03 (br s, 4 H), 8.92 (br s, 4 H), 8.89 (br s, 4 H), 7.86–7.91 (m, 4 H), 7.60 (d, *J* = 7.8 Hz, 2 H), 7.41 (td, *J* = 0.9, 7.0, 7.8 Hz, 2 H), 5.53 (s, 4 H), 4.81 (s, 6 H), 4.18–4.20 (m, 4 H), 3.30–3.32 (m, 4 H), 2.96–2.97 (m, 4 H), 2.87–2.89 (m, 4 H), 2.79–2.81 (m, 4 H), 2.69–2.71 (m, 4 H), –2.82 (br s, 2 H) ppm. ^{13}C NMR (500 MHz cryo, CD_3NO_2): δ = 159.5, 152.8, 144.6, 137.0, 133.8, 131.6, 120.9, 115.9, 113.9, 70.8, 70.7, 69.7, 69.5, 69.4, 69.1 ppm. HRMS: *m/z* calcd: 508.2231 [(M – 2 Cl)/2]; found: 508.2064.