

# Efficient Routes to A<sub>3</sub>B-Type *meso*-(4-Carboxyphenyl) Porphyrin Derivatives

Stanislav I. Presolski, Rob van der Weegen, Jan J. Wiesfeld, and E. W. Meijer\*

Institute for Complex Molecular Systems and Laboratory of Macromolecular and Organic Chemistry, Eindhoven University of Technology, P.O. Box 513, 5600 MB, Eindhoven, The Netherlands

**Supporting Information** 

**ABSTRACT:** A<sub>3</sub>B-type *meso-*(4-carboxyphenyl) porphyrins were prepared either by stepwise coupling of aniline substituents to *meso-*tetrakis(4-carboxyphenyl) porphyrin (TCPP) or by utilizing its partially protected trimethyl ester derivative. We demonstrate the high utility of this building block, which can be synthesized in very good yields by microwave-assisted Me<sub>3</sub>SnOH hydrolysis.



 ${f T}$  he field of supramolecular chemistry has progressed significantly over the past decade, allowing chemists to routinely use weak noncovalent interactions in their design of dynamic, self-healing, and adaptive systems.<sup>1</sup> Many of the advances in one-dimensional architectures have been achieved with small molecules displaying symmetrically arranged binding epitopes that are relatively easy to prepare and avoid unwanted or ill-understood secondary interactions.<sup>2</sup> Breaking the symmetry of the building blocks, however, has been essential in increasing the utility of many supramolecular systems, allowing the marriage of different groups that can work in an ensemble and provide greater structural and functional complexity.<sup>3</sup> Porphyrins have been utilized for the rational design of such next-generation assemblies,<sup>4</sup> which aim to exploit their exceptional redox and photophysical characteristics and well-documented aggregation behavior. These constructs hold promise in the fields of sensing,<sup>5</sup> catalysis,<sup>6</sup> photodynamic therapy,<sup>7</sup> nanodevices,<sup>8</sup> and solar cells<sup>9</sup> where porphyrins have already seen widespread use.

Our initial studies on tetraamide derivatives of *meso*-tetrakis-(4-carboxyphenyl) porphyrin (TCPP) in apolar solvents revealed the reversible formation of long helical stacks, held together by 4-fold hydrogen bonding.<sup>10</sup> The pursuit of more complex assemblies prompted us to prepare  $A_3B$ -type porphyrin building blocks, which deviate as little as possible from the  $D_4$ -symmetric  $A_4$  analogues, in order to minimize any disruption to the supramolecular binding. Therefore, while it was necessary for the two subunits to present different moieties at their periphery, they had to be structurally almost identical. Achieving this hefty goal could not be done by simply reacting TCPP with the two amines of interest or employing statistical condensation of two different benzaldehydes with pyrrole,<sup>11</sup> because both methods would render chromatographically inseparable mixtures. Porphyrin total synthesis<sup>12</sup> and direct functionalization of the *meso*-positions<sup>13</sup> offer pathways to overcome this obstacle, albeit after many reaction steps and with overall low yields, especially when labile functional groups are also present. Hence, we set out to discover synthetically simpler methodologies, and here we report two alternative approaches for the construction of  $A_3B$ -type TCPP derivatives: one involving a stepwise coupling of substituents,<sup>14</sup> and the other utilizing a versatile semiprotected synthon.

Commercially available TCPP was initially treated with 1 equiv of a custom-made aniline, featuring three ether-linked solubilizing aliphatic tails,<sup>10</sup> in the presence of PyBOP and DIPEA. Instead of a mixture of compounds with ratios dictated by probability (32% TCPP, 42% monoamide, 21% diamide, and 5% triamide, 1), the reaction afforded mostly unreacted starting material in addition to the fully substituted porphyrin. The possible culprit behind the departure from the calculated values was the increased solubility, and in turn reactivity, of each subsequent intermediate. Taking advantage of this phenomenon, we then used 3 equiv of the aromatic amine to guarantee a reaction mixture heavily dominated by the tetraamide byproduct, but containing modest amounts of the desired A<sub>3</sub>B-type porphyrin. After a straightforward separation, uncomplicated by the lower members of the  $A_x B_{4-x}$  family, we obtained 1 in 14% yield. This methodology is wasteful to the first substituent that is installed on the porphyrin core, but at the same time is attractive because of the potential for direct subsequent attachment of a wide variety of molecules without protecting group manipulations. Its major drawbacks, however, are the dependency of the product distribution on the electronic and steric nature of the amine being introduced,

Received: January 18, 2014 Published: March 20, 2014 i.e. yield variability, and the need for tedious optimization of the chromatographic step for each new member.



Therefore, we sought to develop a more general strategy for the facile synthesis of A<sub>3</sub>B-type meso-tetra-(4-amidophenyl) porphyrins that relies on partially protected TCPP. We first prepared the tetraacid chloride of the parent macrocycle and treated it with 1 equiv of methanol under dilute conditions. We expected to access a statistically substituted product mixture this time (vide supra), since the solubility difference imparted by the formation of methyl ester was perceived to be minimal. Yet, only the tri- and tetramethyl ester derivatives could be isolated in very low yields after the workup. This observation led us to believe that electronic effects, caused by the extended aromatic system of the meso-carboxyphenyl porphyrin, govern its abnormal reactivity and thus cannot be easily circumvented. Another approach still remained unexplored though, so inspired by the successful partial hydrolysis of trimethyl 1,3,5benzene-carboxylate,<sup>15</sup> we made the tetramethyl ester of TCPP, 2, our starting point to a multipurpose  $A_3B$  building block 3.



Porphyrin 2,<sup>16</sup> which is readily furnished by the Adler method,<sup>17</sup> was treated with 1 equiv of sodium hydroxide in aqueous methanol, giving mostly completely saponified porphyrin (TCPP) alongside unreacted starting material. So we turned our attention to milder bases that typically allow for better reaction control.<sup>18</sup> Lithium hydroxide and potassium trimethylsilanoate<sup>19</sup> (Table 1, entries 2 and 3) were ineffective,

but gratifyingly trimethyltin hydroxide in refluxing 1,2dichloroethane (1,2-DCE) afforded monoacid porphyrin 3 with little overhydrolysis (entry 4).<sup>20</sup> The sluggish reaction (72 h at 95 °C in a sealed vial) was significantly accelerated by higher temperatures (2 h at 150 °C in a high pressure flask) and the addition of two extra equivalents of the base (entry 5). Even though the starting material was not entirely consumed in either case, reaction times longer than the ones reported in Table 1 resulted in loss of product from greater overhydrolysis. When we performed the reaction in a microwave reactor (entries 6 and 7) we needed less Me<sub>3</sub>SnOH and obtained higher yields than with conventional heating. We suspect that the reason is more homogeneous transfer of thermal energy, especially when operating at the gram scale, given that the increase in the rate of hydrolysis is not greater than what can be predicted from the elevated temperature.

The success of our methodology lies not only in finding the appropriate monodeprotection conditions but also in overcoming a common challenge in porphyrin synthesis, the chromatographic separation, where a major hurdle was the coelution of **2** and **3**. We employed a slightly basic solvent system (1% triethyl amine in 1:9 chloroform/heptane) to resolve the product and the starting material on analytical and preparative TLC. But for the large scale reactions we needed a mixture of heptane, chloroform, and ethyl acetate in a 4:4:1 ratio to selectively wash the tetraester **2** from silica gel, before eluting the monoacid **3** with 5% isopropanol/chloroform. This strategy allows for isolation of a valuable A<sub>3</sub>B-type porphyrin intermediate after just one chromatographic step and in up to 52% yield based on recovered starting material.<sup>21</sup>

5,10,15-Tris-(4-methoxycarbonylphenyl)-20-(4'-carboxyphenyl) porphyrin 3 can be coupled to any number of amines, prior to deprotection and further derivatization, which makes it a particularly versatile scaffold. To demonstrate the power of this approach, we prepared porphyrin 4 (Scheme 1) bearing a single acetal that provides a convenient handle for further modification on an otherwise almost indistinguishable aliphatic periphery. The difference between the two anilines we used is quite negligible, which bestows the A<sub>3</sub>B-type porphyrin pseudo  $D_4$  symmetry and the ability to seamlessly intercalate into  $A_4$ porphyrin stacks without jeopardizing any weak bonding interactions. The synthesis of 4 by other methods would be quite formidable, yet, with the triester monoacid 3 at hand, the sequential three-step procedure was accomplished with an 86% overall yield. It is important to point out that substituting Nmethylpyrrolidone (NMP) with dimethylformamide (DMF) or even dimethylacetamide (DMA) in the above reactions consistently gave lower yields,<sup>22</sup> presumably due to the *in situ* formation of solvent-based Vilsmeier intermediates.<sup>23</sup>

entry	base	solvent <sup>a</sup>	amount of $2\ (\text{mg})$	temp (°C)	time (h)	yield <sup><math>b</math></sup> of 3 (%)
1	NaOH	MeOH/H <sub>2</sub> O	42	70	24	$7^c$
2	LiOH	THF/H <sub>2</sub> O	42	95	48	0
3	KOSiMe <sub>3</sub>	Et <sub>2</sub> O	42	25	48	0
4	Me <sub>3</sub> SnOH	1,2-DCE	42	95	72	33 <sup>c</sup>
5	Me <sub>3</sub> SnOH (3 equiv)	1,2-DCE	254	150	2	$20^d$
6	Me <sub>3</sub> SnOH (2 equiv)	1,2-DCE	254	150 <sup>e</sup>	1	$27^d$
7	Me <sub>3</sub> SnOH (2 equiv)	1,2-DCE	1000	150 <sup>e</sup>	1	$42^d$

Table 1. Monohydrolysis of Porphyrin 2

<sup>a</sup>2, 5, and 10 mL for the three different reaction scales. <sup>b</sup>Isolated yield. <sup>c</sup>After preparatory TLC. <sup>d</sup>After column chromatography. <sup>e</sup>Microwave reactor.

# Scheme 1. Synthesis of A<sub>3</sub>B-Type Tetraamide Porphyrin 4



In summary, A<sub>3</sub>B-type monocarboxyphenyl porphyrins can be readily generated from TCPP or from its tetramethyl ester derivative **2**. We have demonstrated the feasibility of a direct synthetic pathway with no protecting groups to monoacid triamide porphyrin **1**. When a diverse pair of substituents must be attached to the *meso*-carboxyphenyl porphyrin core, however, we recommend using intermediate **3**, which can be expediently prepared in very good yields.<sup>24</sup> The operational simplicity of its synthesis and the ease of purification should make it particularly appealing in areas of chemical research where porphyrins with a single addressable attachment point are desired.<sup>25</sup> Further reports on utilizing such molecules in the construction of supramolecular materials will be presented in due time.

## ASSOCIATED CONTENT

## **Supporting Information**

Reaction schemes, detailed experimental procedures, UV-vis, IR, NMR, and MALDI spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

#### AUTHOR INFORMATION

## Corresponding Author

\*E-mail: e.w.meijer@tue.nl.

## Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

The authors would like to thank Drs. Anja Palmans, Elisa Huerta, Matthew Baker, and Miguel Garcia from the Institute for Complex Molecular Systems and Laboratory of Macromolecular and Organic Chemistry, Eindhoven University of Technology for helpful suggestions and discussions. Funding from the Ministry of Education, Culture and Science (Gravity Program 024.001.035), The Netherlands Organization for Scientific Research (NWO), the European Research Council (FP7/2007–2013) ERC Grant Agreement 246829, and the Dutch National Research School Combination Catalysis Controlled by Chemical Design (NRSC-C) is greatly appreciated.

## REFERENCES

(1) Aida, T.; Meijer, E. W.; Stupp, S. I. Science 2012, 335, 813.

(2) (a) de Torres, M.; van Hameren, R.; Nolte, R. J. M.; Rowan, A. E.; Elemans, J. A. A. W. Chem. Commun. 2013, 49, 10787. (b) Zhang, Y.; Chen, P.; Liu, M. Chem.—Eur. J. 2008, 14, 1793. (c) Heeres, A.; van der Pol, C.; Stuart, M.; Friggeri, A.; Feringa, B. L.; van Esch, J. J. Am. Chem. Soc. 2003, 125, 14252.

(3) See examples from benzenetricarboxamides: (a) Viault, G.; Dautrey, S.; Maindron, N.; Hardouin, J.; Renard, P.-Y.; Romieu, A. Org. Biomol. Chem. 2013, 11, 2693. Cyclohexane trisamides: (b) van Bommel, K. J. C.; Stuart, M. C. A.; Feringa, B. L.; van Esch, J. Org. Biomol. Chem. 2005, 3, 2917. Phloroglucinol triamides: (c) Baker, M. B.; Ghiviriga, I.; Castellano, R. K. Chem. Sci. 2012, 3, 1095. Bipyridine discotics: (d) Petkau-Milroy, K.; Sonntag, M. H.; Colditz, A.; Brunsveld, L. Int. J. Mol. Sci. 2013, 14, 21189. Calixarenes: (e) Fischer, C.; Lin, G.; Seichter, W.; Weber, E. Tetrahedron 2011, 67, 5656. Cyclodextrins: (f) Nelson, A.; Stoddart, J. F. Org. Lett. 2003, S, 3783. Phthalocyanines: (g) Cid, J.-J.; Garcia-Iglesias, M.; Yum, J.-H.; Forneli, A.; Albero, J.; Martinez-Ferrero, E.; Vazquez, P.; Grätzel, M.; Nazeeruddin, M. K.; Palomares, E.; Torres, T. Chem.—Eur. J. 2009, 15, 5130.

(4) For reviews, see: (a) Sengupta, S.; Würthner, F. Acc. Chem. Res. **2013**, 46, 2498. (b) Beletskaya, I.; Tyurin, V. S.; Tsivadze, A. Y.; Guilard, R.; Stern, C. Chem. Rev. **2009**, 109, 1659.

(5) Cao, X.; Lin, W.; Yu, Q. J. Org. Chem. 2011, 76, 7423.

(6) Ellis, A.; Gooch, D.; Twyman, L. J. J. Org. Chem. 2013, 78, 5364.
(7) Rhee, J.-K.; Baksh, M.; Nycholat, C.; Paulson, J. C.; Kitagishi, H.; Finn, M. G. Biomacromol 2012, 13, 2333.

(8) (a) Zhang, H.; Liu, Q.; Li, J.; Qu, D.-H. Org. Lett. 2013, 15, 338.
(b) Marois, J.-S.; Cantin, K.; Desmarais, A.; Morin, J.-F. Org. Lett. 2008, 10, 33.

(9) (a) Ambre, R. B.; Chang, G.-F.; Hung, C.-H. *Chem. Commun.* 2014, 50, 725. (b) Mojiri-Foroushani, M.; Dehghani, H.; Salehi-Vanani, N. *Electrochim. Acta* 2013, 92, 315.

(10) (a) Helmich, F.; Lee, C. C.; Nieuwenhuizen, M. M. L.; Gielen, J. C.; Christianen, P. C. M.; Larsen, A.; Fytas, G.; Leclere, P. E. L. G.; Schenning, A. P. H. J.; Meijer, E. W. Angew. Chem., Int. Ed. 2010, 49, 3939. (b) Hoeben, F. J. M.; Wolffs, M.; Zhang, J.; De Feyter, S.; Leclere, P.; Schenning, A. P. H. J.; Meijer, E. W. J. Am. Chem. Soc. 2007, 129, 9819.

(11) Shi, X.; Barkigia, K. M.; Fajer, J.; Drain, C. M. J. Org. Chem. 2001, 66, 6513.

(12) Lindsey, J. S. Acc. Chem. Res. 2010, 43, 300.

(13) Senge, M. O. Chem. Commun. 2011, 47, 1943.

(14) (a) Sforazzini, G.; Turdean, R.; Sakai, N.; Matile, S. *Chem. Sci.* **2013**, *4*, 1847. (b) Ohtani, M.; Saito, K.; Fukuzumi, S. *Chem.—Eur. J.* **2009**, *15*, 9160.

(15) Wallace, J. U.; Chen, S. H. *Ind. Eng. Chem. Res.* **2006**, *45*, 4494. (16) **2** is in fact the synthetic precursor of TCPP.

(17) Adler, A. D.; Longo, F. R.; Finarelli, J. D.; Goldmacher, J.; Assour, J.; Korsakoff, L. J. Org. Chem. 1967, 32, 476.

(18) Nicolaou, K. C.; Estrada, A. A.; Zak, M.; Lee, S. H.; Safina, B. S. Angew. Chem., Int. Ed. 2005, 44, 1378.

(19) Motorina, I. A.; Huel, C.; Quiniou, E.; Mispelter, J.; Adjadj, E.; Grierson, D. S. J. Am. Chem. Soc. 2001, 123, 8.

(20) Furlan, R. L. E.; Mata, E. G.; Mascaretti, O. A. *Tetrahedron* **1998**, 13023.

(21) See Supporting Information for details.

(22) While we did not detect capping of the anilines as reported elsewhere,  $^{23}$  the major impurity of the first coupling reaction was

identified by MALDI as the dimethylamine adduct of **3**. The problem was not ameliorated even when freshly distilled solvents were used.

(23) Murphy, N. S.; Prabhakaran, P.; Azzarito, V.; Plante, J. P.; Hardie, M. J.; Kilner, C. A.; Warriner, S. L.; Wilson, A. J. *Chem.—Eur. I.* **2013**, *19*, 5546.

(24) **2** (1.00 g) and Me<sub>3</sub>SnOH (0.43 g, 2 equiv) were added to a high-pressure vial, dissolved in 1,2-dichloroethane (10 mL), sonicated for 5 min, and then heated in a microwave reactor at 150 °C (200 W, 5 bar) for 1 h. The blood red reaction mixture was filtered through a silica gel plug (washed with 250 mL of 2:1 EtOAc/CHCl<sub>3</sub>) and then concentrated under vacuum, adsorbed on silica, and loaded onto a column (40–63  $\mu$ m SiO<sub>2</sub>, Ø = 10 cm, L = 30 cm). The starting material was eluted with CHCl<sub>3</sub>/heptane/ethyl acetate in a 4:4:1 ratio. Then the solvent composition was changed to 5% *i*PrOH/CHCl<sub>3</sub>, and only the first band was collected. The addition of heptane to the flasks containing the starting material **2** and product **3** turned the solutions cloudy and resulted in the formation of purple (0.190 g) and red (0.415 g) fine precipitates respectively. Yield = 42% (52% brsm).

(25) (a) Kang, B.; Chung, S.; Ahn, Y. D.; Lee, J.; Seo, J. Org. Lett.
2013, 15, 1670. (b) Konev, A. S.; Khlebnikov, A. K.; Nikiforova, T. G.;
Virtsev, A. A.; Frauendorf, H. J. Org. Chem. 2013, 78, 2542. (c) Bandi,
V.; Ohkubo, K.; Fukuzumi, S.; D'Souza, F. Chem. Commun. 2013, 49, 2867. (d) Tanasova, M.; Vasileiou, C.; Olumolade, O. O.; Borhan, B. Chirality 2009, 20, 374. (e) Jiang, M. Y.; Dolphin, D. J. Am. Chem. Soc.
2008, 130, 4236. (f) Balaz, M.; Holmes, A. E.; Benedetti, M.; Proni,
G.; Berova, N. Bioorg. Med. Chem. 2005, 13, 2413. (g) MacMillan, J.
B.; Molinski, T. F. J. Am. Chem. Soc. 2004, 126, 9944.