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Synthesis of a highly soluble superstructured phenanthroline strapped porphyrin

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Abstract—A highly soluble phenanthroline strapped porphyrin is prepared on multigram scale by appropriate functionalization with C_{12} chains after the cyclization of the tetrapyrrolic macrocycle.

1. Introduction

The design and preparation of 5,15-diaryl and 5,10,15,20-tetraaryl porphyrin architectures to be used either as enzyme models, or in the preparation of new materials often faces the challenge of the tetrapyrrolic macrocycle's poor solubility.[1] Sulfonation of the aryl groups,[2] quaternization of pyridine substituents,[3] or introduction of neutral hydrophilic groups[4,5] performed a posteriori to the formation of the tetrapyrrolic macrocycle have provided nice ways to access water soluble material.[6] The preparation of sophisticated porphyrin derivatives soluble in organic solvents is usually achieved by the use of aldehydes bearing long alkyl chains or substituted dipyrrylmethanes in Lindsey's modern version of Adler's condensation.[7] Such an approach has the advantage of limiting the number of synthetic steps performed on the porphyrin itself.

For the last decade, we have made extensive use of a phenanthroline strapped porphyrin **1**, which was prepared by cyclization, at low concentration in dichloromethane, of a phenanthroline dialdehyde derivative with an unsubstituted dipyrrylmethane in the presence of trifluoroacetic acid.[8] The efficiency of the condensation (45–60%) has turned **1** into a starting material for several ongoing projects in our group, however its low solubility in dichloromethane (4 mg/mL) has always been a drawback for further functionalization. The introduction of xylyl groups provided a slight solubility increase, but attempts to use more soluble intermediates such as *m*-xylyl dipyrrylmethane to obtain the derivative **2** were unsuccessful. Compound **2** had to be prepared from **1** in two steps in 60% yield (overall) by functionalization of the free *meso* positions (10,20).[9] In addition, because the most interesting features of **1** and **2** lie in the use of the cavity defined by the phenanthroline strap,[10] functionalization of these structures requires that the *meso* positions remain unhindered, thus forbidding solubility increase involving their substitution (Fig. 1). All attempts to use more soluble phenanthroline intermediates resulted in extremely poor cyclization yields and inextricable mixtures of porphyrin derivatives. Previous failure of cyclizations using alkyl dipyrrylmethanes strongly suggested that poor solubility of the porphyrinogen intermediate was a thermodynamic well essential to the high cyclization yield. However, no other successful cyclization experiments were available to support this hypothesis. We were thus prompted to perform the condensation reaction with a poorly

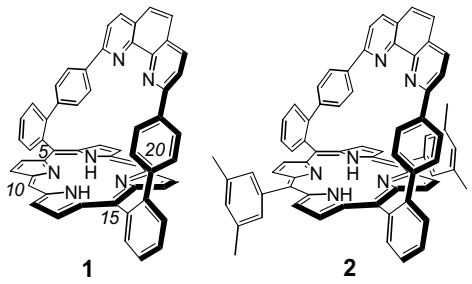

Figure 1. Two phenanthroline strapped porphyrin derivatives poorly soluble in organic solvents.

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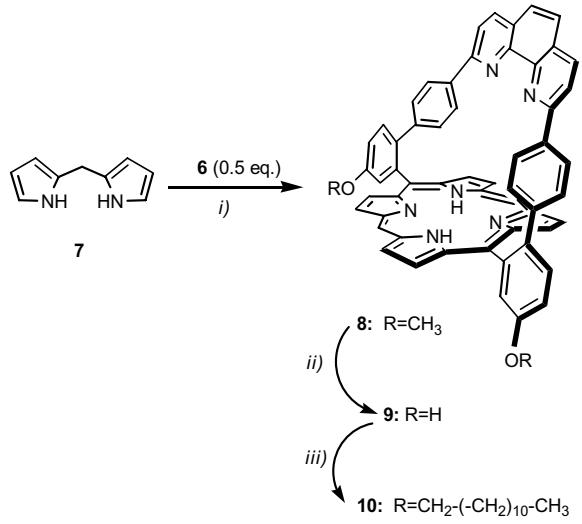
soluble phenanthroline aldehyde derivative, which incorporated two sites that could be used to add solubilizing alkyl chains after porphyrin formation.

The 2,9-di-(4-bromophenyl)-1,10-phenanthroline derivative **4** has been prepared as previously described in the literature.[11] Dioxolane formation on the 2-bromo-5-methoxy benzaldehyde was achieved in 89% in the presence of ethylene glycol in toluene containing *p*-toluene sulfonic acid as a catalyst. Further lithiation at low temperature (−78 °C) with *n*-butyllithium, and quenching of the intermediate with tri-*n*-butylborate afforded the boronic acid **5** in 81% after acidic treatment. Suzuki coupling (2 M K_2CO_3, toluene, MeOH, $Pd(PPh_3)_4$, 90°C, 1 day) of the dibromide **3** and 2 equiv of boronic acid **5** afforded the dialdehyde **6** in 71% yield (Scheme 1).

The dipyrrylmethane **7** was prepared by reported methods[12] and condensed under dilute conditions in a 2/1 stoichiometry with the dialdehyde **6** to afford a unique porphyrin derivative **8** in 60% yield. Interestingly, over repeated cyclization reactions, the average yield for **8** tends to be 5–10% higher than for **1** under identical conditions. The dimethoxy derivative **8** is slightly less soluble than the unsubstituted **1**, and the high yields obtained at this stage tend to confirm our hypothesis regarding the thermodynamically favored formation of insoluble cyclic material. After drying by repeated evaporation with toluene, the poorly soluble porphyrin **8** (3 mg/mL) was then treated with BBr_3 (1 M in CH_2Cl_2) in refluxing CH_2Cl_2 for 4 h to cleave the methoxy groups. The corresponding dihydroxy derivative **9** is insoluble in most organic solvents, except for hot dimethylformamide. Alkylation of **9** with 1-bromododecane was performed in DMF in the presence of K_2CO_3, to afford the porphyrin derivative **10** in 90% yield (two steps) (Scheme 2). The high solubility of **10** (40 mg/mL), combined with its gram scale availability certainly opens new possibilities regarding further functionalization of the unsubstituted 10, and 20 (*meso*) positions.

In conclusion, the porphyrin **10** is available on gram scale, is highly soluble in organic solvents, and bears two *meso* positions available for further functionalization. This is a rare combination in the area of strapped porphyrins. Development of soluble self-assembled photonic devices incorporating **10** as a building block is under progress.



Scheme 2. Porphyrin **8** formation. Reagents and conditions: (i) a. TFA, CH_2Cl_2, 25 °C, 20 h, b. 10 equiv DDQ, 25 °C, 2 h; (ii) 50 equiv BBr_3, CH_2Cl_2, 40 °C, 4 h; (iii) 7.3 equiv $Br–(–CH_2)_{11}–CH_3$, K_2CO_3, DMF, 80 °C, 20 h.

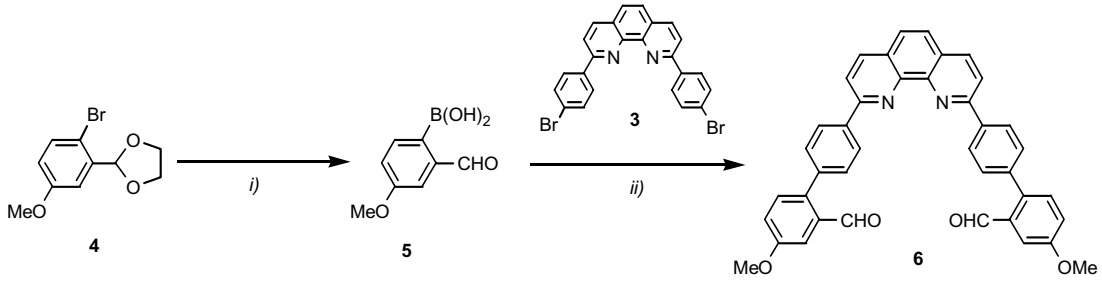
2. Experimental

2.1. 2-(2-Bromo-5-methoxy-phenyl)-[1,3]dioxolane (4)

A mixture of 2-bromo-5-methoxybenzaldehyde (14.5 g, 68 mmol), ethylene glycol (5 mL, 88 mmol), and *p*-toluenesulfonic acid (380 mg, 2 mmol) in 230 mL of toluene was heated to reflux. The water formed during the reaction was eliminated with a 'Dean Stark' apparatus. After 15 h the solution was washed twice with a 2 M solution of aqueous K_2CO_3, dried over anhydrous Na_2SO_4, and the solvent was evaporated. Column chromatography (60–200 μm SiO_2, cyclohexane/ethyl acetate 4:1, diameter 4.5 cm, h = 30 cm) afforded 15.5 g (60 mmol, 89%) of **4** as a yellow-brown oil that was used without further purification. ^1H NMR ($CDCl_3$, 300 MHz): 7.45 (d, J = 8.7 Hz, 1H), 7.16 (d, J = 3.1 Hz, 1H), 6.79 (dd, J_1 = 8.7 Hz, J_2 = 3.1 Hz, 1H), 6.05 (s, 1H), 4.21–4.03 (m, 4H), 3.81 (s, 3H).

2.2. 2-Formyl-4-methoxy-phenylboronic acid (5)

An argon flushed solution of dioxolane **4** (15.5 g, 60 mmol) in 200 mL of freshly distilled diethyl ether was cooled to −78 °C. *n*-Butyl lithium (1.6 M in



Scheme 1. Synthesis of **6**. Reagents and conditions: (i) a. 1.1 equiv *n*-BuLi, Et_2O, −78 °C, 45 min, b. 1.3 equiv $B(OBu)_3$, −78 °C, 30 min, 25 °C, 2 h, c. H_3O^+, H_2O; (ii) $Pd[P(Ph_3)_4]$, K_2CO_3, toluene/MeOH/H_2O, 90 °C, 24 h.

hexane, 42 mL, 66 mmol) was added dropwise while maintaining the temperature below −70 °C. After stirring the mixture for 45 min at −78 °C, tributyl borate (22 mL, 79 mmol) was added dropwise, keeping the temperature below −55 °C. After stirring for 30 min at −78 °C, the solution was warmed to room temperature over 2 h. Acid–base extraction of the reaction mixture afforded 8.7 g (48 mmol, 81%) of **5** as a grayish solid. This product was also used without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz): 9.88 (s, 1H), 8.23 (d, J = 8.5 Hz, 1H), 7.44 (d, J = 2.7 Hz, 1H), 7.20 (dd, J = 8.5 Hz, J' = 2.7 Hz, 1H), 6.96 (s, 2H), 3.93 (s, 3H).

2.3. Dialdehyde (6)

To a suspension of 2,9-bis(4-bromophenyl)-1,10-phenanthroline (7.7 g, 15.7 mmol), boronic acid **5** (7 g, 39 mmol), and K_2CO_3 (43 g, 311 mmol) in 250 mL of toluene, was added 80 mL of water and 80 mL of methanol. The mixture was Ar flushed and $Pd(PPh_3)_4$ (200 mg, 0.17 mmol) was added. After stirring at 85 °C for 20 h, 200 mL of a solution of 15% ethyl acetate in CH_2Cl_2 was added to the reaction mixture and the organic suspension was washed three times with brine, then dried with toluene (azeotropic distillation of residual water). The crude product was recrystallized in boiling toluene to yield 6.6 g (16 mmol, 71%) of **6** as a brown solid. Melting point: 239–241 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): 10.12 (s, 2H), 8.61–8.58 (m, 4H), 8.46 (d, J = 8.5 Hz, 2H), 8.29 (d, J = 8.5 Hz, 2H), 7.92 (s, 2H), 7.68–7.65 (m, 4H), 7.58–7.55 (m, 4H), 7.31 (dd, J = 8.6 Hz, J' = 3 Hz, 2H), 3.97 (s, 6H). Elemental analysis: % calculated for $C_{40}H_{28}N_2O_4 + 0.5C_7H_8 + 0.5CH_3COOCH_2CH_3$: C, 79.11; H, 5.25; N, 4.06; found: C, 78.74; H, 5.53; N, 4.06.

2.4. Dimethoxy-phenanthroline strapped porphyrin (8)

A solution of dialdehyde **6** (278 mg, 0.46 mmol), dipyrrylmethane (140 mg, 0.46 mmol) and trifluoroacetic acid (1 mL) in 1.6 L of dichloromethane was stirred for 20 h under argon. Dichloro-dicyano-quinone (900 mg), was added and the mixture was refluxed for 2 h. The solution was neutralized with 20 mL of triethylamine, washed three times with water, and dried over Na_2SO_4 prior to the evaporation of the solvent. The porphyrin was purified by chromatography over Al_2O_3 (neutral, activities II–III, diameter 4 cm, h = 10 cm). Elution with CH_2Cl_2 and evaporation of the solvent afforded 243 mg (62% yield) of **8** as a red-brownish powder. Melting point: >300 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 10.21 (s, 2H), 9.34 (d, J = 4.5 Hz, 4H), 9.07 (d, J = 4.5 Hz, 4H), 8.34 (d, J = 2.8 Hz, 2H), 8.02 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 8.8 Hz, 2H), 7.58 (dd, J = 8.8 Hz, J' = 2.8 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 7.54 (s, 2H), 6.71 (d, J = 8.6 Hz, 4H), 6.52 (d, J = 8.6 Hz, 4H), 4.18 (s, 6H), −3.12 (s, 2H). UV–visible in CH_2Cl_2 λ_{max} (ε in $M^{-1}cm^{-1}$): 300 (63,000), 339 (56,000), 415 (231,000), 507 (15,000), 540 (4000), 579 (5000), 635 (1000). Elemental analysis: % calculated for $C_{60}H_{44}N_6O_2 + 0.5CH_2Cl_2$: C, 78.64; H, 4.40; N, 9.41; found: C, 78.24; H, 4.76; N, 9.42.

2.5. Dihydroxy-phenanthroline strapped porphyrin (9)

1 M boron tribromide solution (30 mL, 30 mmol) in dry dichloromethane was added dropwise under argon to a solution of porphyrin **8** (880 mg, 0.59 mmol) in 100 mL of dry dichloromethane. The mixture was refluxed for 4 h under argon and then a portion of 20 mL of methanol was added. The solvent was removed and the crude product was dissolved in CH_2Cl_2/EtOH (10:4). The solution was washed once with water and twice with a 2 M solution of aqueous K_2CO_3, and then dried over Na_2SO_4. Evaporation of the solvent afforded crude **9** as a dark-red powder. Due to its insolubility this product was used without further purification.

2.6. Didodecanoxy-phenanthroline strapped porphyrin (10)

Crude porphyrin **9** (0.59 mmol) was reacted with an excess of 1-bromo-dodecane (588 mg, 4.4 mmol) in 200 mL of DMF with K_2CO_3 (815 mg). After stirring the mixture at 80 °C for 20 h, the solvent was partially removed. Water (200 mL) was added, and the product was filtered over Celite. The crude porphyrin **10** was taken in dichloromethane and the solution was dried over Na_2SO_4. The solvent and the excess of 1-bromododecane were distilled under reduced pressure (10 mm Hg). Porphyrin **10** was then purified by chromatography over Al_2O_3 (neutral, activities II–III, diameter 2 cm, h = 20 cm). Elution with dichloromethane and evaporation of the solvent afforded 1.08 g of **10** (91% yield for the last two steps) as a purple powder. Melting point: 255–265 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): 10.14 (s, 2H), 9.24 (d, J = 4.7 Hz, 4H), 8.98 (d, J = 4.7 Hz, 4H), 8.33 (d, J = 2.7 Hz, 2H), 7.95 (d, J = 8.4 Hz, 2H), 7.80 (d, J = 8.6 Hz, 2H), 7.51 (m, 6H), 6.69 (d, J = 8.6 Hz, 4H), 6.35 (d, J = 8.6 Hz, 4H), 4.32 (t, J = 6.8 Hz, 4H), 1.99 (m, 4H), 1.5–1.2 (m, 18H), 0.88 (m, 6H), −2.91 (s, 2H). UV–visible in CH_2Cl_2 λ_{max} (ε in $M^{-1}cm^{-1}$): 302 (64,000), 338 shoulder (56,000), 416 (233,000), 507 (14,000), 541 (4000), 579 (5000), 635 (1000). Elemental analysis: % calculated for $C_{82}H_{88}N_6O_2 + 0.5CH_2Cl_2$: C, 80.44; H, 6.96; N, 6.99; found: C, 80.78; H, 7.07; N, 6.66. Mass spectrometry (MALDI TOF): mass calculated for $M+H^+$: 1159; found: 1159.23.

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