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Synthesis and Supramolecular Properties of a Novel Octaphosphonate Porphyrin

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Dedicated to Professor Dr. M. S. Shingare

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Two complementary routes were developed for preparing novel octaphosphonate porphyrins. The use of protected/deprotected phosphonate-substituted precursors in the rational synthesis gave an overall yield 16 %. A more streamlined synthetic path gave 21 % overall yield of the target molecule. Octaphosphonate porphyrin possesses promising properties in supramolecular aggregate formation with cyclam. Cofacial reversible self-assembly of a *meso*-substituted octaphosphonate porphyrin with cyclam yields micrometer-long nanowires with a height of about 1–1.5 nm. The resulting wires were characterized by UV/Vis absorption, emission and atomic force microscopy and transmission electron microscopy.

Introduction

The formation of self-assembled materials with well-defined shapes and dimensions presents both a great challenge and opportunity with potential application in catalysis, molecular electronics and materials science.[1] It is well known that the porphyrin macrocycle provides a useful nanometer-sized rigid and planar building block for the construction of well-defined assemblies.[2] Judicious choice of outer periphery functionality can lead to geometric tectons displaying 90° and 180° geometries,[3] or cofacial arrangements that manifest themselves as nanowires, nanotubes, helical ribbons or liquid crystalline aggregate topographies.[4,5] Pseudo-1D topologies are of particular interest as molecular wires for energy, electron and charge transport.[6] Recent reports suggest that the introduction of hydrogen-bonding groups to the periphery of the porphyrin play an important role in determining the final mode of aggregation.[7] The question lies in the identification and use of such moieties for efficient self-assembly.

Phosphate groups are essential to metabolism and biosynthesis, gene regulation, muscle contraction, cellular energy generation and antibiotic resistance.[8] Phosphate receptor binding in aqueous solution requires polytopic interactions by hydrogen bonding, usually in the presence of polyamines.[9] Furthermore, the interaction of phosphonates with Zr^{IV} salts has been shown to be a useful strategy to form stable (irreversible) fibrous materials.[10] Although many multiporphyrin systems have been reported in the literature,[1–7,10] there are only few examples in which the phosphonate group of the porphyrin of fascinating molecular architectures is self-assembled on the surface[7d,10] or attached to the surface[11] for studies of molecular-based information storage on oxide surfaces. New methodologies to functionalize porphyrins with phosphonate substituents other than normal aromatic groups are of particular interest for the preparation of nanomaterials. Reported herein is the novel synthesis of a *meso*-substituted porphyrin bearing an octaphosphonate group and the preparation of discrete supramolecular nanowires on the basis of its self-assembly with cyclam from aqueous solutions on a gold surface, without the need of metal ion additives. To the best of our knowledge, this is the first report of the synthesis of octaphosphonate porphyrin and its self-assembly with cyclam.

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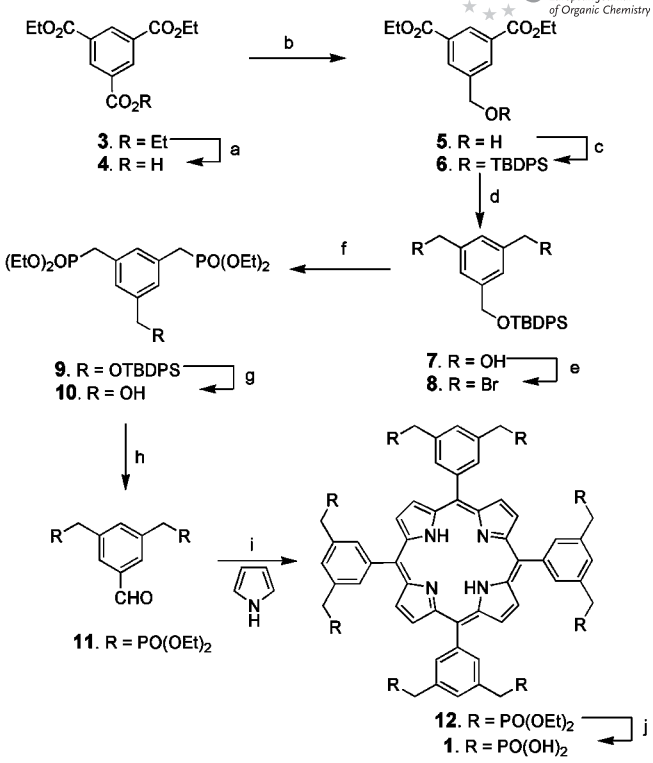
Results and Discussion

Synthesis of the Porphyrin-Based Molecule Bearing Peripheral Octaphosphonate Groups

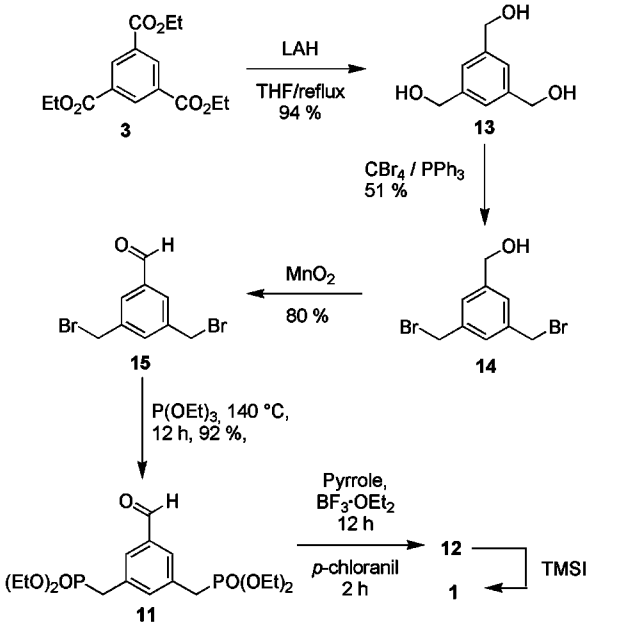
The synthesis strategy employed to prepare targeted octaphosphonate porphyrin **1** was focused toward careful functional group protection to achieve a high overall yield (Scheme 1). Synthesis of **1** began by performing a mono deprotection of commercially available triethyl benzene-1,3,5-tricarboxylate (**3**) to afford 3,5-bis(ethoxycarbonyl)-benzoic acid (**4**) by treatment with KOH (0.9 equiv.), followed by selective reduction of the free carboxylic acid by using BH_3·DMS to give **6** in 78% yield over two steps. The benzylic alcohol of **5** was then TBDPS protected (99% yield), allowing reduction of the two ethyl ester sites of **6** to proceed smoothly whilst retaining the TBDPS masked alcohol. Diol **7** was brominated by using carbon tetrabromide and triphenylphosphane to afford dibrominated product **8** in 78% yield. Conversion of **8** into diphosphonate ethyl ester **9** was achieved in high yield by heating in neat triethyl phosphite. The TBDPS protecting group of **9** was then removed with TBAF and oxidized to desired aldehyde **11** by using PCC in 59% yield after chromatographic separation. Porphyrin synthesis was then performed by first treating the aldehyde with an equimolar amount of pyrrole along with a catalytic amount of BF_3·OEt_2 to form the porphyrinogen in situ, followed by the addition of *p*-chloranil to oxidize the newly formed tetraaza macrocycle to desired octaethyl ester porphyrin **12** in 21% yield after column chromatography. Deprotection of the octaethyl ester of porphyrin **12** was executed by simple hydrolysis with trimethylsilyl iodide at –40 °C in dry dichloromethane followed by aqueous workup to give targeted porphyrin **1** in 95% yield.

A more streamlined synthetic path was later considered to minimize handling time, as detailed in Scheme 2. Rather than relying on careful protection for the synthesis of benzaldehyde **11**, a more direct route was taken that required chromatographic separation at the bromination step. This method had been reported previously in the formation of selective polyarene dendrimers bearing electron-donating and electron-withdrawing moieties through Heck and Horner–Wadsworth Emmons reactions by using the corresponding phosphonate with aromatic aldehyde.[12] Complete reduction of tricarboxylate **3** by using $LiAlH_4$ was first performed to give the tribenzyl alcohol in 97% yield after aqueous workup. Bromination with the use of carbon tetrabromide and triphenylphosphane led to a mixture of mono-, di- and tribrominated products, which could be separated by column chromatography to give desired dibromo compound **14** in 51% yield.

It should be noted that the monobrominated product remains synthetically useful, as it may be further brominated to the dibromo adduct later. The benzylic alcohol of **14** was cleanly oxidized to aldehyde **15** by using freshly prepared MnO_2 in an 80% yield, and finally installation of the phosphonate ester functionality at the 3,5-positions was quantitatively performed by using the same protocol as for **9**



Scheme 1. Synthesis of octaphosphonate porphyrin **1**. Reagents and conditions: (a) KOH, EtOH/THF, 12 h; (b) BH_3·$(CH_3)_2S$, 0 to 60 °C, N_2, overnight, THF; (c) TBDPSCl, DMAP, Py, 0 °C to room temp., 24 h, DCM; (d) LAH, N_2, 3 h, THF; (e) PBr_3, diethyl ether, 0 °C to room temp., 4 h; (f) triethyl phosphite, 120 °C, 12 h; (g) TBAF, THF, room temp., overnight; (h) PCC (pyridinium chlorochromate), DCM, room temp., 2 h, (i) BF_3·OEt_2, DCM, room temp., Ar, 14 h, *p*-chloranil 2 h; (j) TMSI (trimethylsilyl iodide), $CHCl_3$, –40 °C to room temp., 1 h.



Scheme 2. Alternative route for the synthesis of phosphonate aldehyde **11**.

(Scheme 1). Treatment of **15** with triethyl phosphite at 140 °C afforded diphosphonate ethyl ester **11** in high isolated yield. Comparison of the overall yield of aldehyde **11** clearly shows that the latter synthesis protocol is the preferred method, as it provides rapid access to **12** with minimal handling in a higher isolated yield (26 vs. 16% overall).

Supramolecular Self-Assembly of Octaphosphonate Porphyrin with Cyclam

The absorption spectrum of octaphosphonate **1** (0.01 mmol) in water at pH 7.0 with protonated phosphonate groups (pK_a = 7.8) has a strong Soret band at 440 nm and four weak Q bands at 599 and 655 nm (Figure 1a, broken line). The addition of 0.1 M NaOH to this solution (pH 9) brings about distinct changes in the absorption spectrum of compound **1**, as the Soret band is shifted to 418 nm and the Q bands are shifted to 518, 553, 583 and 636 nm (Figure 1a, solid line). At pH 3–7, the phosphonate group and the internal NH are protonated, and upon addition of sodium hydroxide to the solution we observed deprotonation of the internal NH. Upon addition of cyclam (0.01 mmol at pH 9), the absorption band shifted to longer wavelength with broadening of the peaks and loss of fine structure accompanied by a decrease in intensity (Figure 1b, broken line). The Soret band shifted to 422 nm and the four Q bands shifted to 521, 561, 584 and 644 nm (Figure 1b, broken line). In the Soret band region, the redshift is a sign of J-type aggregate formation, whereas the blueshift is a sign of H-aggregate formation.[13]

The evolution of the absorption spectrum of compound **1** with cyclam addition indicated the formation of a J-type aggregate, with an angle between the molecule transition dipole moment. The turbidity of the solution after the addition of cyclam also indicated the formation of an aggregate. Furthermore, the fluorescence intensity dramatically decreased, which supports the aggregation of porphyrin–cyclam (Figure 1b, inset). UV/Vis spectroscopy (in water) indicated a long wavelength shift by 4 nm and a decrease in the intensity with loss of fluorescence, which can be attributed to the formation of larger aggregates than just π–π-stacked dimers or oligomers. Therefore, atomic force microscopy (AFM) and transmission electron microscopy (TEM) were performed to further investigate the self-assembly of **1** in aqueous medium.

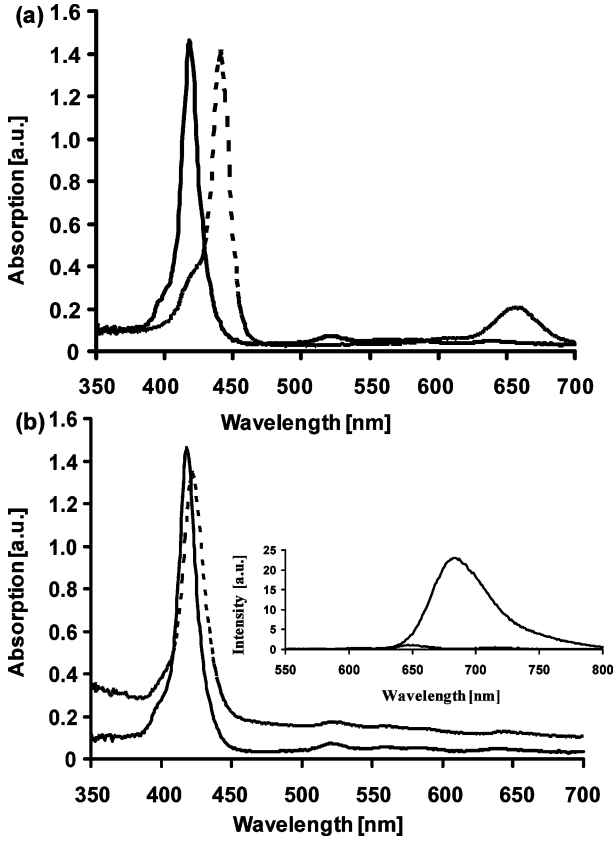


Figure 1. (a) UV/Vis absorption spectra of porphyrin **1** (1×10^{-4} M) in H_2O at pH 7.0 (broken line) and pH = 9.0 (solid line); (b) upon addition of cyclam **2** with porphyrin **1** at pH 9.0 (broken line) without cyclam (solid line). Inset shows emission of **1** with (broken line) and without cyclam (broken line), respectively.

AFM and TEM of Supramolecular Self-Assembled Phosphonate Porphyrin and Cyclam

Surface patterning experiments were performed by mixing equimolar solutions (1×10^{-4} M) of porphyrin **1** in 0.1 M aqueous NaOH and cyclam **2** in water and then applying them, after ultrafiltration, to a freshly prepared gold surface.[7d] An example of the obtained AFM images is shown in Figure 2, which clearly displays wire-like aggregates. The ratio of the diameter and height of the nanowires formed by **1** and **2** was estimated to be approximately 1–1.5 nm with typical lengths of 1–12 μM (for height profiles, see the Supporting Information; Figure S1A, c and d). The collected images show no evidence for the nanowires to align further with one another once formed.

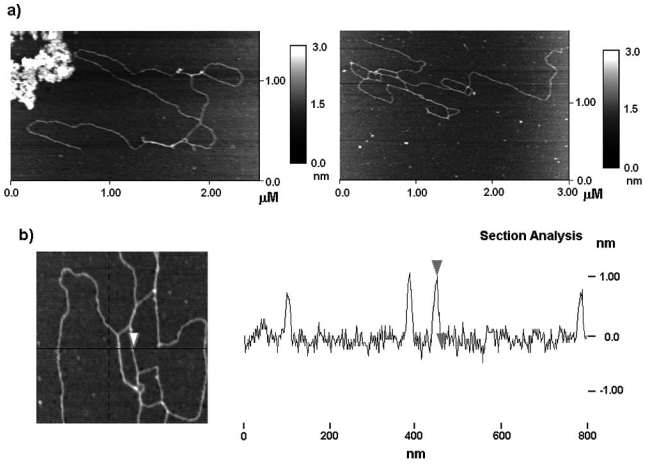


Figure 2. (a) AFM topography images of the self-assembled (phosphonato)porphyrin–cyclam structure deposited on a freshly prepared gold surface; (b) section analysis showing 1–2 nm heights of wires. All samples were measured at room temperature in air.

The orientation of the porphyrinic units to the Au(111) surface is proposed to be planar; however, a canted domino-like stacking arrangement is also plausible given that the obtained images do not give full molecular resolution. The growing process initiated by stepwise additions and phosphonate **1** and cyclam **2**, which are stabilized by weak hydrogen bonds and van der Waals forces, arrange at the ends of the growing fibres co-facially. However, a deck-of-cards arrangement is also plausible, wherein the porphyrins are more parallel to the surface. This may provide evidence for the fact that hydrophilized surfaces provide more space for π–π interactions (between porphyrin and surfaces). One may expect to obtain a 3D self-assembly because of the octaphosphonate group of the porphyrin with cyclam, but cross links between the porphyrin and cyclam fibres do not occur because of the rigidity of the building blocks; only co-facial growth was observed (Supporting Information; Figure S1A, c and d).[14] Nanowires formed between **1** and **2** were air stable and were found to be stable for several months. The fact that neither porphyrin **1** nor cyclam **2** deposited individually on the gold surface, which would lead to a regular surface pattern under the same preparative conditions, infers that the interaction between **1** and **2** is crucial to the formation of the nanowires (Supporting Information, Figure S1a). At pH values below 9.0, no aggregation was detected, because the phosphonic groups are fully protonated, but the concomitant inner nitrogen protonation (inducing two central positive charges) hinders aggregation with cyclam (Supporting Information, Figure S1A, b).

Furthermore, TEM images of a sample of an equimolar (1×10^{-4} M) aqueous (pH 9) solution of **1** and **2** deposited on a carbon grid stained by 1% phosphotungstate also provided direct visualization of self-assembled porphyrin–cyclam entities that were several nanometers long (Figure 3). In this case, the aggregated structures are formed in which strands are entangled with one another. Attempts to obtain individual nanowires by dilution of the deposition mixture or to detect termination of the wire sections and thus determine the individual strand lengths failed. We have observed stepwise growth of nanowires in TEM with different time interval (Supporting Information, Figure S2B).

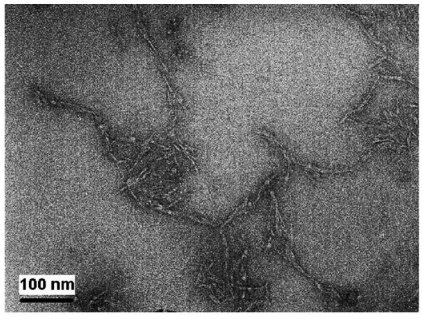
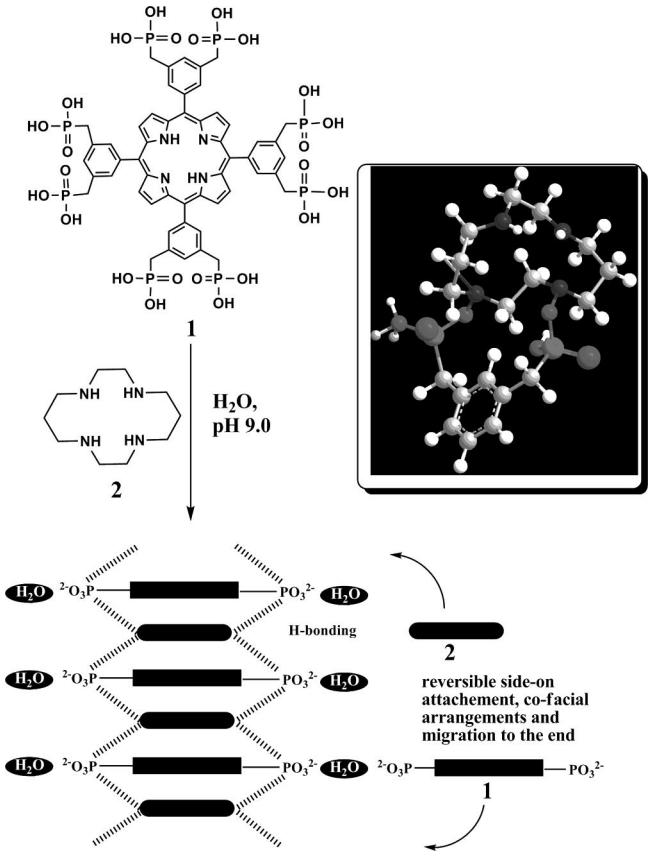


Figure 3. Transmission electron microscopy (TEM) images of submicrometer long porphyrin–cyclam aggregated wires on a carbon grid (negative stain: 2% phosphotungstate). The bar indicates the scale.

Proposed Model of Supramolecular Self-Assembly

We propose that this arrangement is driven by noncovalent interactions, where the cyclam macrocycle bridges the porphyrin units, as graphically depicted in Scheme 3. The spacing of the NH sites along the propyl section of the cyclam approximately match the positions of the phosphonate groups, which presumably drive the linear growth of the wires (see inset in Scheme 3).



Scheme 3. Systematic illustration of the hydrogen-bonded self-assembly of octaphosphonate porphyrin **1** and cyclam **2** with a cofacial arrangement. Inset shows interaction of phosphonate with cyclam through H-bonding after MM2 calculation.

Conclusions

In summary, two complementary routes were developed to prepare octaphosphonate porphyrins. The use of protected/deprotected phosphonate-substituted precursors in the rational synthesis of porphyrin **1** gives an overall yield 16%. A more streamlined synthetic path gives a 21% overall yield of the target molecule. Novel octaphosphonate porphyrin possesses promising properties in supramolecular aggregate formation with cyclam. This has led to the development of a novel strategy for the formation of nanowires based on the interaction of phosphonate porphyrins with cyclam on gold surfaces and on carbon grids. This new approach opens up some appealing opportunities, especially as it seems easily applicable to a large variety of porphyrinic

architectures on surfaces. The presented methodology is expected to provide a basis for the synthesis of other molecular nanostructures on surfaces, as the ionic components may be easily varied. This facilitates the positioning of the nanowires at electrode junctions and may offer a convenient method to fabricate more complex arrangements. We are also currently producing the porphyrin phosphonate fibres from zinc and tin(IV) complexes to measure electric conductivities of cation and anion π–radical stacks.[15]

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were recorded with a Varian Gemini (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR), a Varian Mercury (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR) or a Varian Unity Inova (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR) spectrometer. Chemical shifts are reported in ppm downfield from tetramethylsilane (TMS; δ = 0 ppm) at room temperature using $CDCl_3$ as solvent and internal standard unless otherwise indicated. Abbreviations used for splitting patterns are s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet and br. = broad, with coupling constants (J) given in Hz. IR spectra were recorded with a Perkin–Elmer 1600 FTIR (UATR) spectrometer; band intensities are indicated as s (strong), m (medium) and w (weak). Electrospray ionization (ESI) mass spectrometry was performed with a Q/TOF Ultima GLOBAL mass spectrometer (Micromass, Manchester, UK) equipped with a Z-spray source. Elemental analyses were carried out using a Perkin–Elmer 2400 instrument. Unless stated otherwise, column chromatography was carried out on silica gel 60 (Fluka, 40–63 μM). $[\alpha]_D^{20}$ values were recorded with a Jasco P-1030 Polarimeter, and melting points were recorded on a heating table from Reichert (Austria). Analytical TLC was performed on silica gel 60 (Fluka, 0.2 mM). Other reagents were purchased from Acros or Aldrich and were used without further purification. THF was dried with sodium metal wire, and pyridine was dried with 4 Å molecular sieves.

3,5-Bis(ethoxycarbonyl)benzoic acid (4):[16] Triethyl benzene-1,3,5-tricarboxylate (**3**; 28.2 g, 0.096 mol) was combined with absolute EtOH (75 mL) and THF (50 mL) in a 250-mL, three-necked flask. The mixture was heated to reflux, thus ensuring dissolution of the entire solid. Powdered KOH (8.7%, 5.3 g, 84.0 mmol) was then added portionwise over a 30 min period at room temperature. The solution was then heated at reflux for 12 h. The reaction mixture was concentrated in vacuo to afford a thick slurry, which was partitioned between water and CH_2Cl_2. The aqueous phase was washed with CH_2Cl_2, and concentrated HCl (8.5 mL) was added to precipitate the product. The product was recrystallized from absolute EtOH to afford **4** as white crystals (18.9 g, 76%). M.p 152–153 °C (ref.[16] 153–154 °C). ^{1}H NMR (300 MHz $CDCl_3$, 25 °C): δ = 1.18 (t, J = 7.1 Hz, 6 H), 4.21 (q, J = 7.1 Hz, 4 H), 8.50 (d, 1 H, Ar), 8.53 (d, 2 H, Ar), 11.02 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 14.8, 61.9, 129.4, 135.7, 136.2, 165.7, 169.4 ppm. MS (FAB–, Xe): m/z = 266.4 $[M]^{+\cdot}$. $C_{13}H_{14}O_6$ (266.4): calcd. C 58.64, H 5.30; found C 58.39, H 5.49.

Diethyl 5-(Hydroxymethyl)isophthalate (5):[16] Tricarboxylate **4** (5 g, 18.7 mmol) was dissolved in THF (30 mL) in a 250-mL, round-bottomed flask, and the mixture was cooled to 0 °C in an ice bath. $BH_3{\cdot}(CH_3)_2S$ (2.0 M in THF, 102 mL, 20.4 mmol) was added over a period of 3 h. After completion of addition, the reaction mixture was heated at 60 °C overnight. The reaction mixture was neutralized by the addition of H_2O/glacial acetic acid (1:2). The reaction mixture was dissolved in hot ethanol and precipitated into water to retrieve a white powder. A final recrystallization from ethanol yielded **5** as white crystals (3.6 g, 78%). M.p. 79 °C (ref.[16] 78 °C). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.24 (t, $^3J_{H,H}$ = 7.1 Hz, 6 H), 3.45 (s, 1 H, OH), 4.67 (s, 2 H), 4.33 (q, J = 7.1 Hz, 4 H), 8.15 (s, 2 H, Ar), 8.23 (s, 1 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 14.1, 61.3, 66.2, 129.4, 130.5, 136.3, 141.9, 165.7 ppm. IR (KBr): $\tilde{\nu}$ = 3417 (O–H stretching of primary alcohol), 3100 (C–H stretching of aromatic), 2984–2873 (C–H stretching of methylene), 1724 (C=O stretching of ester), 1445–1371 (C–H bending of methylene and methyl group), 1242 (C–O stretching of ester), 1024 (C–O stretching of primary alcohol) cm^{-1}. MS (EI): m/z = 253.2 $[M + H]^+$. $C_{13}H_{16}O_5$ (252.0): calcd. C 61.90, H 6.34; found C 62.03, H 6.39.

Diethyl 5-[(*tert*-Butyldiphenylsilyloxy)methyl]isophthalate (6):[17,18] To a solution of **5** (5 g, 19.82 mmol), DMAP (0.126 g) and pyridine (3.2 mL) in CH_2Cl_2 (40 mL) under an atmosphere of argon and cooled to 0 °C was added dropwise TBDPSCl (8.15 g, 29.4 mmol, 1.5 equiv.), and the mixture was stirred for 24 h at room temperature. The reaction mixture was quenched with 1 M HCl (20 mL). The aqueous layer was washed with CH_2Cl_2 (200 mL). The combined organic layer was then washed with water (2 × 50 mL), dried with Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. Flash chromatography [SiO_2, $CHCl_3$/hexane (1:1)] gave **6** as a colourless oil (9.7 g, quant.). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.98 (s, 9 H, $SiMe_3$), 1.4 (t, $^3J_{H,H}$ = 7.0 Hz, 6 H), 4.45 (q, J = 7.0 Hz, 4 H), 4.80 (s, 2 H), 7.47–7.36 (m, 6H Ar), 7.70–7.67 (m, 4 H, Ar), 8.25 (s, 2 H, Ar), 8.55 (s, 1 H) ppm. ^{13}C-NMR: (75 MHz, $CDCl_3$, 25 °C): δ = 26.8, 61.2, 64.7, 127.8, 129.2, 129.6, 129.8, 130.9, 131.2, 133.1, 134.8, 135.2, 135.5, 141.9, 165.9 ppm. MS (EI): m/z = found 491.8 [M + H]. $C_{29}H_{34}O_5Si$ (490.2): calcd. C 70.99, H 6.98; found C 70.87; H 6.84.

{5-[(*tert*-Butyldiphenylsilyloxy)methyl]-1,3-phenylene}dimethanol (7):[19] Isophthalate **6** (15.4 g, 3.16 mmol) in dry THF (50 mL) was added dropwise to a slurry of lithium aluminium hydride (1.80 g) in dry THF (150 mL) under an atmosphere of argon. The reaction mixture was stirred at room temperature for 3 h and it turned green. The reaction mixture was quenched, followed by hydrolysis, using methanol (10 mL) and water (30 mL). The mixture was filtered, and the white precipitate was washed several times with methanol (3 × 10 mL) followed by THF (2 × 10 mL). The combined liquid phases were evaporated under reduced pressure to give a yellow oil. Recrystallization from hexane gave white crystals of **7** (11.05 g, 85%). M.p. 93 °C (ref.[19] 93 °C). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.01 (s, 9 H, $SiMe_3$), 3.34 (s, 2 H, CH_2OH), 4.41 (s, 4 H), 5.01 (s, 2 H), 7.20 (s, 2 H), 7.22 (s, 1 H), 7.39 (m, 6 H), 7.69 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 19.8, 26.9, 65.0, 65.4, 123.9, 124.1, 127.7, 129.7, 133.4, 135.6, 141.2 ppm. IR (KBr): $\tilde{\nu}$ = 3239 (O–H stretching of alcohol), 3070 (C–H stretching of phenyl ring), 2929, 2856 (C–H stretching of methylene group), 1471–1309 (C–H bending of methylene), 1105 (C–O stretching of primary alcohol) cm^{-1}. MS: (EI): m/z = 407 $[M + H]^+$. $C_{25}H_{30}O_3Si$ (406): calcd. C 73.85, H 7.44; found C 73.78, H 7.68.

[3,5-Bis(bromomethyl)benzyloxy](*tert*-butyl)diphenylsilane (8):[19,20] A solution of PBr_3 (3.03 g, 11.2 mmol) in dry diethyl ether (50 mL) was slowly added to a cooled (0 °C) solution of **7** (3.248 g, 8 mmol) in dry diethyl ether (120 mL). Once all the PBr_3 solution was added the reaction mixture was warmed to room temperature and stirred for a further 4 h. After this period of time, water (50 mL) was added and the aqueous layer was extracted with diethyl ether (200 mL). The organic layers were combined, dried with Na_2SO_4

and filtered. The solvent was evaporated under reduced pressure. Purification of the crude mixture was performed by column chromatography [SiO_2, hexane/ethyl acetate (9:1)] to yield white crystals of **8** (4.26 g, 78%). M.p. 90 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.98 (s, 9 H, $SiMe_3$), 4.54 (s, 4 H), 4.74 (s, 2 H), 7.27 (s, 2 H, Ar), 7.68 (m, 4 H); 7.28 (s, 1 H, Ar), 7.39 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 19.3, 26.8, 31.6, 33.0, 33.9, 64.9, 126.7, 127.8, 128.1, 129.8, 135.6, 138.3 ppm. MS: (EI): *m*/*z* = 533, 530. $C_{25}H_{28}Br_2OSi$ (532): calcd. C 56.40, H 5.30; found C 56.37, H 5.16.

Tetraethyl {5-[(*tert*-butyldiphenylsilyloxy)methyl]-1,3-phenylene}bis-(methylene)diphosphonate (9):[21] Triethyl phosphite (5 mL) and **8** (2.70 g, 5 mmol) were combined in a round-bottomed flask with stirring under an atmosphere of argon at 120 °C for 12 h. The excess triethyl phosphite was then removed under reduced pressure. The crude, oily product was purified with column chromatography [SiO_2, $CHCl_3$/MeOH (95:5)]. Two columns were performed to achieve pure compound **9** as a colourless oil (2.54 g, 77%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.99 (s, 9 H), 1.25 (t, $^3J_{H,H}$ = 7.1 Hz, 12 H), 3.12 (s, 2 H), 3.11 (s, 2 H), 4.21 (m, 8 H), 4.74 (s, 2 H), 7.10 (m, 2 H), 7.18 (br., 1 H), 7.39 (m, 6 H), 7.68 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 16.3, 26.8, 40.3, 68.9, 126.1, 129.3, 130.0, 130.7, 132.5, 134.2, 141.7 ppm. MS: (FAB–, Xe): *m*/*z* = 646.6 $[M + H]^+$.

Tetraethyl [5-(Hydroxymethyl)-1,3-phenylene]bis(methylene)diphosphonate (10):[22] Tetrabutyl ammonium fluoride (14 mL, 13 mmol) was added to solution of **9** (6 g, 9.28 mmol) in THF (80 mL), and the reaction mixture was left to stir overnight. The reaction mixture was quenched by the addition of glacial acetic acid (2 mL), and the solvent was then removed in vacuo. The crude product was purified by column chromatography (SiO_2, 1% MeOH in $CHCl_3$) to give **10** as a white solid (3.64 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.25 (t, $^3J_{H,H}$ = 7.1 Hz 12 H), 3.17 (s, 2 H), 3.20 (s, 2 H), 4.00 (m, 8 H), 4.58 (s, 2 H), 7.09 (s, 2 H), 7.15 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 16.9, 40.4, 62.3, 65. 5, 126.7, 130.5, 132.8, 141.3 ppm. IR (KBr): $\tilde{\nu}$ = 3417, 3121, 2981, 2877, 1758, 1452, 1369 1248, 1029 cm^{-1}. MS: (FAB–, Xe): *m*/*z* = 409.4 $[M + H]^+$.

Diethyl 5-Formylisophthalate (11):[23] To a suspended solution of pyridinium chlorochromate (2.85 g, 13 mmol) in CH_2Cl_2 (20 mL) was added a solution of **10** (3.6 g, 8.8 mmol) in CH_2Cl_2 (10 mL), and the reaction mixture was stirred for 2 h. The reaction mixture was diluted with diethyl ether (200 mL), and the solvent was decanted from the solid residues, which were washed again with ether (200 mL). The organic layer was collected, dried with Na_2SO_4 and evaporated under reduced pressure. Flash column chromatography [SiO_2, $CHCl_3$/MeOH (10:0.5)] gave pure compound **11** as a colourless oil (2.10 g, 59%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.27 (t, $^3J_{H,H}$ = 7.4 Hz, 12 H, 4 × CH_3CH_2), 3.21 (s, 4 H), 3.98–4.07 (m, 8 H, 4 × CH_3CH_2), 7.53 (br. s, 1 H, Ar), 7.72 (m, 2 H, Ar), 9.91 (s, 1 H, CHO) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 16.1, 36.9, 62.1, 127.4, 133.9, 136.4, 137.7, 191.3 ppm. IR (KBr): $\tilde{\nu}$ = 2817 and 2733 (aldehyde C–H stretching), 2982–2872 (C–H stretching of methylene group), 1699 (C=O stretching of aldehyde), 1477–1367 (C–H bending of methylene), 1249 (C–O stretching of aldehyde) cm^{-1}. MS: (FAB–, Xe): *m*/*z* = 407.6 $[M + H]^+$.

5,10,15,20-Tetrakis-[3,5-bis(diethoxyphosphorylmethyl)phenyl]porphyrin (12):[24] A mixture of CH_2Cl_2 (600 mL), **11** (2.03 g, 5 mmol) and pyrrole (0.335 g, 5 mmol) was stirred under an atmosphere of nitrogen at room temperature in the dark for 15 min. To this solution, $BF_3{\cdot}OEt_2$ (0.265 mL) in CH_2Cl_2 (10 mL) was added, and the reaction mixture was left to stir for 14 h. *p*-Chloranil (1.2 g) was added and the mixture was stirred for another 2 h, after which time the reaction mixture had turned a deep violet colour. After standing for 30 min, the solution was concentrated and silica gel (10 g) was added. The slurry was dried to afford a dark powder that was then poured onto the top of a chromatography column of silica. The desired compound was eluted using a solvent mixture of chloroform/acetonitrile/methanol (10:10:1). A second column was needed to give the desired porphyrin **12** as a red/purple solid (474 mg, 21%). $C_{84}H_{118}N_4P_2O_{24}$ (1814.6). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = –2.8 (s, 2 H, 2-NH), 1.28 (t, $^3J_{H,H}$ = 7.1 Hz 48 H, CH_3CH_2), 3.58 [d, ^2J = 22.0 Hz, 16 H, $CH_2P(O)(OEt)_2$], 4.2–4.35 (m, 32 H, CH_2CH_3), 7.89 (s, 4 H, Ar), 8.50 (br. s, 8 H, Ar), 8.81 (s, 8 H Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 16.6, 33.4, 62.4, 121.9, 128.1, 134.9, 138.8, 145.9, 190.4, 196.1 ppm. MS: (FAB–, Xe): *m*/*z* = 1816.3 $[M + H]^+$.

5,10,15,20-Tetrakis [3,5-Bis(diphosphonoxylatophosphorylmethyl)-phenyl]porphyrin (1):[25] To a solution of **12** (200 mg, 1×10^{-4} M) in chloroform (20 mL) cooled to –40 °C was added trimethylsilyl iodide (0.26 mL) with a syringe needle. The reaction mixture was kept at –40 °C for 30 min, then warmed to room temperature and stirred for another 1 h. Water (5 mL) and triethylamine (1.5 mL) were added, and after stirring for 5 min the solvents were removed under vacuum to give desired compound **1** as a purple solid (150 mg, 95%). ^{1}H NMR (400 MHz, D_2O, 25 °C): δ –2.8 (s, 2 H, 2-NH) 3.16 [m, 16 H, $CH_2P(O)(OH)_2$], 7.63 (s, 4 H), 7.97 (br. s, 8 H), 9.32 (br. s, 8 H) ppm. ^{13}C NMR (125 MHz, D_2O, 25 °C): δ = 34.2, 122.8, 128.6, 136.2, 139.8, 144.7, 190.1, 196.8 ppm. HRMS (MALDI-TOF): calcd. for $C_{51}H_{55}N_4O_{24}P_9$ 1386.7586; found 1386.6793.

Self-Assembled Standard Porphyrin Solution for Atomic Force Microscopy (AFM): Porphyrin **9** (0.01 mmol) was dissolved in 0.1 M NaOH (10 mL). Cyclam (0.01 mmol) was dissolved in water (10 mL) at pH 7.0. Both samples were mixed together in 1:1 ratio and the resulting solution was stirred for 1 h, deposited in a freezer at 5 °C and after 2 weeks the aggregated side products were removed by simple ultrafiltration and applied as a AFM probe on freshly prepare gold surface.

Atomic Force Microscopy: AFM images were recorded using a MultiMode IIIa scanning probe microscopy with Entender Module (Digital Instruments, Inc., Santa Barbara, CA) that was operated in the dynamical modus. Olympus etched silicon cantilevers were mostly used with a typical resonance frequency in the range 200–400 MHz and spring constant of 42 N/m. All samples were measured at room temperature in air environments. The sample was first adjusted with an optical light microscopy (Nano Scope, Optical Viewing System). The microscope was than mounted on a vibration isolation table (Halcyonics, MOD-1) and under a glass bell for reduction of acoustical noise. The typical scanning speed was 1 line s^{-1}. Data analysis was performed after plane-fit, height measurements based on the cross-sectional profiles.

Transmission Electron Microscopy (TEM): A droplet (5 mL) of the freshly sonicated aqueous solution (above self-assembled standard porphyrin–cyclam solution) was placed on hydrophilized carbon films on copper wire grids (60 s plasma treatment at 8 W using a BALTEC MED 020 device). Excess fluid was blotted off and air dried on the grids. Microscopy was carried out by using a Philips CM12 TEM operated at 100 kV accelerating voltage at a low electron dose (<100 e $Å^{-1}$).

Supporting Information (see footnote on the first page of this article): ^{1}H NMR spectra of important compounds; AFM and TEM images of self-assembled octaphosphonate porphyrin **1** with cyclam **2**.

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