Large-scale synthesis of alkyne-linked tripodal porphyrins *via* palladium-mediated coupling conditions†

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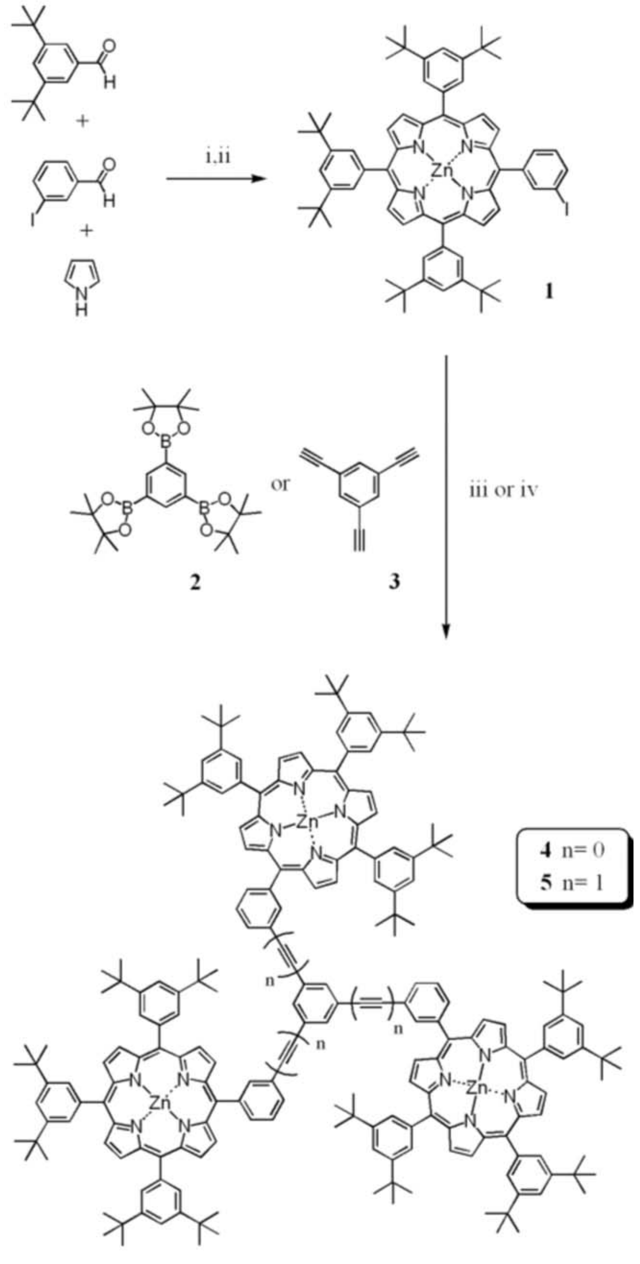
Suzuki and Sonogashira couplings have been used in short and efficient sequences to give access to a new family of porphyrin trimers on a practical scale.

The photophysical and electrochemical properties of covalently-linked arrays of porphyrins are of great interest in a variety of biomimetic,[1] supramolecular[2] and materials arenas.[3] However, they present a substantial synthetic challenge, in part because solubility problems and the difficulties of separating incompletely coupled intermediates become increasingly serious.[4] We have previously described a variety of cyclic porphyrin oligomers, but even under optimised templating conditions, the routes have been long, separation difficult and ultimately only small amounts of materials were available for the study of their properties.[5] The key strategies for avoiding this problem are (i) to ensure that the chromatographic properties of the starting materials and products are different,[6] and (ii) to employ reliably high-yielding carbon–carbon bond-forming reactions.[7] We now report the short, efficient and large scale syntheses of a family of tripodal porphyrin trimers using these strategies. Modelling, spectroscopy and a synchrotron X-ray diffraction study indicate these new systems have significant potential for molecular recognition.

Scheme 1 shows the overall synthetic strategy. In this porphyrin family, the sole difference between the "small trimer" **4** (*i.e.* $n = 0$) and the "large trimer" **5** (*i.e.* $n = 1$) is the type of linkage that connects the three porphyrin components to the central benzene core. The previously unreported zinc porphyrin precursor **1**, bearing the desired substitution pattern at the *meso* positions, is required for the syntheses of both trimeric porphyrins. 3,5-di-*tert*-butylbenzaldehyde was selected to give better solubility to the porphyrins and, more importantly, facilitate the purification process by giving a more distinct polarity difference between **1** and unwanted products generated under the coupling conditions. In view of the statistical distribution of products generated in the acid-catalysed condensation, the reaction conditions were optimised (*i.e.* reaction time and stoichiometric ratio of starting materials), leading to the development of a gram-scale access to **1**, as detailed in the supporting information.†



Scheme 1 Reagents and conditions: (i) Propionic acid, 6 h, reflux. (ii) $Zn(OAc)_2 \cdot 2H_2O$, $CHCl_3/MeOH$, 16%. (iii) For the synthesis of **4** ($n = 0$): $Pd(PPh_3)_4$, Na_2CO_3, toluene/EtOH/H_2O (10 : 4 : 3), 4 d, 80 °C, 80% (iv) For the synthesis of **5** ($n = 1$): $Pd_2(dba)_3$ (dba = dibenzylideneacetone), $AsPh_3$, CH_2Cl_2/Et_3N (2 : 1), 3 d, 25 °C, 91%.

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† Electronic Supplementary Information (ESI) available: Synthesis and characterisation data, NMR labelling schemes, calculated gas-phase conformations of **4** and crystal structures of **1** and **2**. See DOI: 10.1039/b515902d

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Synthesis of the zinc trimer **4** demands a three-fold Suzuki coupling reaction between **1** and triboronic ester **2**, performed in the presence of a catalytic amount of $Pd(PPh_3)_4$ in a biphasic system. Linker **2** was obtained as the boronic ester intermediate in the preparation of 1,3,5-benzenetriboronic acid.[8] To promote the formation of the desired trimeric product over partially-coupled species, 3.3 equiv. of **1** were used with respect to 1 equiv. of **2**, giving a yield of 80%. Sonogashira coupling between **1** and 1,3,5-triethynylbenzene (**3**) was catalysed by $Pd_2(dba)_3$ (with $AsPh_3$ employed as cocatalyst), leading to the formation of **5** in a yield of 91%. Production of undesirable species could be suppressed by the use of excess porphyrin monomer (5 equiv. of **1** per 1 equiv. of **3**).

In each case, the trimers were separated by preparative thin layer chromatography; further purification was achieved by subsequent recrystallisation. The preparation of both trimers was performed on a 100 mg scale using these optimal conditions.† Conventional spectroscopic techniques have been employed for characterisation of all new species, while X-ray crystallography provided solid state evidence for the structures of **1**, **2** and **5**.§

Fig. 1 shows the aromatic region of the ^1H NMR spectra of **4** and **5**. ^1H–^1H COSY and NOESY experiments were carried out to assist with the assignment of the spectra. Attention should be directed to the singlets (coloured in red) observed at 8.32 and 7.72 ppm in **4** and **5**, respectively, which correspond to the protons of the benzene cores. The sharp signals in **4** and **5** confirm the overall C_3 symmetry of conformations adopted by both trimers at room temperature. This is due to the fast equilibration of the potential conformers of **4** and **5** on the NMR timescale as a result of rotational motion along the bonds connecting the porphyrin and core spacer.

We were attracted by the rich host–guest chemistry and rate-accelerating abilities of some previously published rigid porphyrin cages.[9] The present less rigid tripodal porphyrin systems could be advantageous in recognition processes as they are geometrically less demanding and more responsive when selecting potential guests. To explore the new porphyrin systems as supramolecular hosts, the conformations of **4** and **5** in the gas phase and solution ($CDCl_3$) were examined. Also, the solid state conformation of **5** was obtained in order to help gain an understanding of the rotational behaviour of the porphyrin moieties around the porphyrin–central benzene linkages.

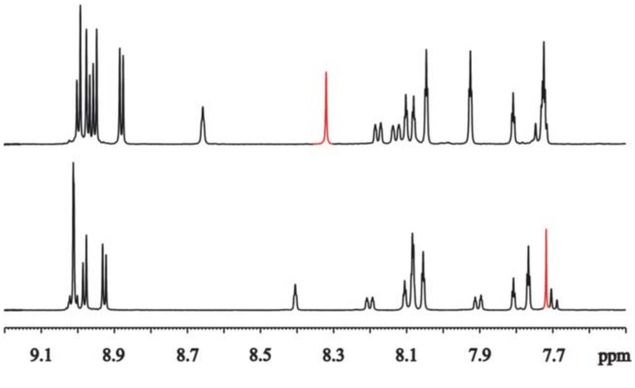

Fig. 1 Aromatic region of the ^1H NMR spectra (500 MHz, 298K) of **4** (above) and **5** (below) in $CDCl_3$. The singlets coloured in red correspond to the protons of the central benzene linkers.

Fig. 2 The crystal structure of the zinc porphyrin trimer **5**. Hydrogen atoms and solvent molecules (coordinating to the metal centres and free) are omitted for clarity. (Key: Grey = carbon, blue = nitrogen, purple = zinc). Clockwise from left: Zn(1), middle: Zn(2) and right: Zn(3).

Variable temperature ^1H NMR experiments on the trimers show some broadening of the singlet resonances corresponding to the benzene cores. Unfortunately the coalescence temperature could not be reached upon cooling to 218 K in $CDCl_3$. This provides evidence of the effectively "energy-barrier-free" rotational freedom along the covalent linkages in the given temperature range.

The solid state structure of **5**, determined by X-ray diffraction using synchrotron radiation, also sheds light on the conformationally-flexible nature of the zinc porphyrin trimer (Fig. 2). The molecular structure shows that two of the three arms of the tripodal framework deviate by 15.7 and 12.0° below the central aromatic plane; the third one, bearing Zn(1), being oriented almost perpendicular to this plane (*ca.* 75.4°). Inspection of the CPK models indicates that this geometry best accommodates the strain induced by the extreme bulk of the outer sphere, populated by a total of eighteen (rotationally-disordered) *tert*-butyl groups. The bending of the framework is clearly seen in the differing orientations of the porphyrin planes: the porphyrins bearing Zn(3) and Zn(2) centres deviate from planarity by only 6.1° and both zinc-coordinated MeOH molecules are pointing towards the inside of the cavity thus formed. The best planes between these two porphyrins and a third porphyrin, bearing Zn(1), are at angles of 48.8 and 50.2°, respectively.

Two of the zinc centres are coordinated to MeOH, rendering each of these metal centres in square pyramidal geometries. The distances from the zinc atoms to the methanol oxygen atoms, Zn(2)–O(1) and Zn(3)–O(2), are 2.079(10) and 2.111(10) Å, respectively. Each arm of the central aromatic unit bears zinc-substituted porphyrin groups, each porphyrin being further substituted with three highly bulky aromatic units at the *meso* positions. Within each porphyrin unit, the nitrogen atoms are nearly coplanar [maximum deviations from the best plane 0.07 Å (ring bearing Zn(1)), 0.12 Å (ring bearing Zn(2)) and 0.10 Å (ring bearing Zn(3))]; the zinc atoms are situated at a mean distance of 0.24 Å above the N4 planes (*i.e.* Zn(1): 0.10 Å, Zn(2): 0.32 Å and Zn(3): 0.29 Å). This is within the range observed for this displacement in mononuclear zinc porphyrins. For example, in

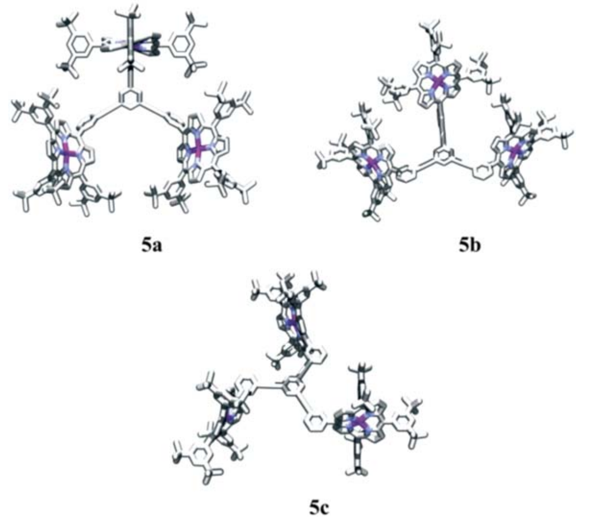

Fig. 3 Three energy-minimized gas phase conformations of the large porphyrin trimer **5** (PM3 level, Spartan'04).[10] (Key: Grey = carbon, blue = nitrogen, purple = zinc).

precursor **1**, the MeOH-coordinated Zn(1) atom is situated 0.27 Å above the best N4 plane.

Semi-empirical calculations (PM3) have also been performed to further explore the highly flexible nature of the zinc porphyrin trimeric systems.[10] Fig. 3 shows three gas-phase PM3 optimised geometries of three thermodynamically-stable conformers of **5** found in the gas phase: bowl-shaped **5a**, propeller-shaped **5c**, and **5b** with a conformation resembling the crystal structure. The relative differences in the heats of formation of **5a**, **5b** and **5c** are less than 20 kJ mol^{-1}. Negligible differences are observed between the bowl-shaped and propeller-shaped conformers of **4**.

Preliminary results suggest that trimer **5** has the ability to bind to C_{60} molecules in solution; the ^{1}H NMR spectrum (500 MHz, $CDCl_3/CS_2$ (9 : 1), 25 °C) of a 1 : 1 mixture of **5** and C_{60} showing several significant shifts. Details will be reported elsewhere.

In summary, we provide practical routes to a new family of tripodal porphyrin arrays. Extensive studies of the new systems become possible as a result of their large-scale preparation. The electron rich π surfaces of porphyrins in conjunction with their axial binding abilities mean that a variety of encapsulation processes are possible with the porphyrin trimers. More importantly, the rotationally flexible nature of the systems will enable the selection of a wider range of guest molecules.

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Notes and references

§ X-ray quality crystals of **1** were obtained from a CH_2Cl_2 solution layered with MeOH, and for **2**, were grown by slow evaporation of an MeOH solution. Data for **1** and **2** were collected at 180 K on a Nonius Kappa CCD with graphite monochromated Mo-K$_\alpha$ radiation (λ = 0.71073 Å). A concentrated solution of **5** ($CHCl_3$/MeOH (2 : 3)) yielded extremely small, deep-red, needle-shaped crystals. Crystallographic data for **5** were collected using the synchrotron radiation source at Station 9.8, Daresbury SRS, UK, on a Bruker SMART CCD diffractometer. The structures of **1**, **2** and **5** were solved by direct methods using the program programs SIR92.[11] The refinements (on F) and graphical calculations were performed using the CRYSTALS[12] program suite. *Crystal data.* **1·MeOH·CH$_2$Cl$_2$**: $C_{70}H_{80}Cl_2IN_4OZn$, M = 1256.62, Z = 2, triclinic, space group P-1, a = 10.9085(2), b = 15.7116(3), c = 20.0954(4) Å, α = 101.3092(7), β = 90.3507(8), γ = 91.7091(12)°, U = 3375.52(11) Å^3, T = 180(2) K, μ = 0.943 mm^{-1}. Of 138647 reflections measured, 49864 were independent (R_{int} = 0.08). Final R = 0.0949 (9164 reflections with $I > 3\sigma(I)$) and wR = 0.0816. **2**: $C_{24}H_{39}B_3O_6$, M = 456.00, Z = 4, orthorhombic, space group $P2_12_12_1$, a = 10.3474(2), b = 12.5764(2), c = 20.7829(3) Å, α = 90, β = 90, γ = 90°, U = 2704.54(8) Å^3, T = 180(2) K, μ = 0.076 mm^{-1}. Of 23365 reflections measured, 3111 were independent (R_{int} = 0.05). Final R = 0.0389 (1832 reflections with $I > 3\sigma(I)$) and wR = 0.0457. **5·MeOH·2H$_2$O**: $C_{218}H_{234}N_{12}O_3Zn_3$, M = 3218.48, Z = 4, monoclinic, space group $P2_1/c$, a = 45.66(5), b = 14.605(15), c = 30.04(3) Å, β = 90.50(10)°, U = 20032(36) Å^3, T = 150 (2) K, μ = 0.409 mm^{-1}, synchrotron radiation λ = 0.68920 Å. Of 63297 reflections measured, 12041 were independent (R_{int} = 0.05). Final R = 0.0790 (5680 reflections with $I > 3\sigma(I)$) and wR = 0.0874. CCDC 288530–288532. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b515902d

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