Macrocyclic pentamers functionalised around their periphery as potential building blocks†

Seong Nam,a David C. Warea and Penelope J. Brothersa,*b

The elaboration of a five-fold symmetric macrocyclic aromatic pentamer bearing peripheral benzyloxy and hydroxyl groups is described. These could be used to explore further functionalisation for use as pentagonal building blocks. The internal fluorine-substituted macrocycle has been prepared via a one-pot procedure which is an improvement on the stepwise chain growth approach reported in the literature.

Introduction

Shape-persistent macrocycles enjoy a wide range of uses facilitated by their well-defined features.1 Planar (or near-planar) macrocycles with full or partial conjugation typically exhibit 2 to 6-fold (or higher) symmetry. They may bear functional groups on the periphery that improve solubility, play a role in their function, or direct intermolecular interactions and the formation of nano-architectures. Depending on the size of the macrocycle, the internal functionality may be significant in directing the formation of the macrocycle, or may be optimised for metal coordination or other guest recognition. Their syntheses demonstrate many approaches, from traditional macrocyclic chemistry using Schiff-base formation or template synthesis to more contemporary routes such as click chemistry and metathesis reactions.2–5 Although the field is well established, there is still relatively little chemistry focussed on tailoring the peripheral substitution chemistry for particular applications where precisely controllable, supramolecular interactions are desired. As an example, organisation of shape-persistent macrocycles on a surface may be controlled by macrocycle–surface interactions with the edge-to-edge macrocycle packing determined by the symmetry of the macrocycle and interactions between the peripheral substituents.6 This works well when the macrocycle symmetry packs naturally in a plane (e.g. rectangular, square, triangular or hexagonal units7) but when this is not the case there are additional challenges.

A case in point is 5-fold symmetry where complete coverage of a plane by pentagons cannot be achieved as evidenced by the particular properties of Penrose tiling patterns. Planar organisation of shape-persistent molecules with 5-fold symmetry has received some attention. Deposition of corannulene derivatives on Cu(111) surfaces produces hexagonal patterns where the symmetry of the underlying surface directs the ordering of the molecules, despite their 5-fold symmetry.8,9 Ferrocene carboxylic acid, although not itself having 5-fold symmetry, demonstrated regions of 2D quasicrystalline, Penrose tile ordering of molecules on a Au(111) surface directed by supramolecular interactions between the ferrocene carboxylic acid groups.10 Combining these two approaches suggests that appending supramolecular recognition functionality on the periphery of 5-fold symmetric, shape-persistent molecules might be useful for directing their packing, especially with the object of reproducing quasicrystalline surface ordering. This approach has been considered from a design point of view, although the molecules proposed have not been achieved experimentally.11,12

Four classes of planar, shape-persistent molecules with 5-fold symmetry have been reported in the literature (Fig. 1). They comprise 5 aryl or pyridine groups connected by two-atom linkers. Zeng et al. have reported five-fold symmetric macrocyclic aromatic pentamers13–16 and macrocyclic pyridine pentamers17 which contain aryl–amide links; the former have OMe, OEt and macrocyclic pyridone pentamers13 which contain aryl–amide links; the former have OMe, OEt or F groups in the interior positions while the pyridone pentamers have hydrogen-bonded carbonyls. Campestarenes have imine linkages and an internal hydrogen-bonded network of amine NH and OH groups.18,19 Cyanostars20,21 and alkyne-linked macrocycles22 are cyanostilbene and phenylene ethynylene pentamers with internal C–H groups. All are planar (or near-planar) and significantly conjugated. The peripheral functional groups in all of these molecular pentagons are typically, H, alkyl, ether or ester groups, none of which are optimised for supramolecular interactions. We recently published the peripheral elaboration of campestarenes containing peripheral pyridine and carboxylic acid functions designed for this purpose.23 In this paper we focus on the five-fold symmetric macrocyclic aromatic pentamers (Fig. 1a) and approaches to a macrocycle bearing peripheral hydroxyl groups (R = OH) which could potentially be used to explore further functionalisation for use as a pentagonal building block. In addition, we have prepared the internal fluorine-substituted macrocycle (X = F) via a one-pot procedure as an improvement on the stepwise chain growth approach reported in the literature.24,25

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Results and discussion

The benzyloxy macrocyclic pentamer (1) was synthesised using the one-pot procedure developed in Zeng’s group by condensation of the benzyloxy-substituted precursor 12. This procedure had been previously reported for macrocycles substituted with H, Me, OCHMeCO2H, OCHMeCO2Et, 4-C6H4N, 4-C6H4CN, 4-C6H4CO2H); and (d) cyanostar (R = tBu, isoamyl, SiPh3, Si(iPr)3, Br, OMe, OCH2CO2H, OCHMeCO2H, OCHMeCO2Et, 4-C6H4N, 4-C6H4CN, 4-C6H4CO2H); and (d) cyanostar (R = tBu, C6H5).

Scheme 1  Synthesis of benzyloxy (1) and hydroxy macrocyclic pentamers (2): (i) conc. H2SO4, MeOH, reflux, 48 h, 83%; (ii) BnBr in CHCl3/MeOH, K2CO3, CH2Cl2, reflux, 48 h, 40%; (iii) Bi(NO3)3, Montmorillonite K10, THF, 1 h, 31%; (iv) Mel, K2CO3, DMF, 50 °C, 12 h, 99%; (v) 3 M NaOH, MeOH, reflux, 2 h, 99%; (vi) Pd/C, H2, 40 °C, 450 kPa, 18 h, 96%; (vii) Pt/C, H2, MeOH, 18 h, 97%; (viii) POCl3, Et3N, MeCN, 12 h, 14%; (ix) BBr3, CH2Cl2, 0 °C, 12 h.

De-protection of 1 to give 2 via hydrogenation was unsuccessful under all the conditions investigated, varying the catalysts (Pd/C, Pt/C or a mixture of both), temperature and pressure of H2. This suggests that the reactivity of the peripheral groups has been significantly reduced after cyclisation and consequently the macrocyclic pentamers are rather more inert than anticipated. An alternative route is to use BBr3 to remove the benzyl group, although, as reported by Zeng et al., BBr3 can also de-methylate the inner methoxy methyl groups. This was successful for the preparation of 2 although the crude product mixture contained pentamers missing some internal methoxy groups. Purification of 2 was achieved by analytical reverse-phase HPLC eluting with water for 5 min and 0–100% of methanol over 25 minutes. The other species missing one or two inner methoxy groups could also be separated during the purification process.

The internal methoxy groups in the macrocyclic pentamers protrude above and below the plane of the macrocycle which is

Fig. 1 Planar, shape-persistent molecules with 5-fold symmetry: (a) macrocyclic aromatic pentamers (X = OMe, OEt, F; R = OC6H17, OMe, OiPr, Me); (b) macrocyclic pyridone pentamers (R = tBu, C6H5, CH3, CH2Et, (CH2CH2O)2Me, (CH2CH2O)3Me, CH2C6H3); (c) campestar-ene (R = tBu, isoamyl, SiPh3, Si(iPr)3, Br, OMe, OCH2CO2H, OCHMeCO2H, OCHMeCO2Et, 4-C6H4N, 4-C6H4CN, 4-C6H4CO2H); and (d) cyanostar (R = tBu, C6H5).
less ideal for their use as building blocks for supramolecular nanostructures.\textsuperscript{11,12} Zeng’s group has reported a number of pentamers in which the internal positions are occupied by fluoro rather than methoxy groups.\textsuperscript{24,25} These were prepared by the laborious stepwise chain growth method originally reported for the methoxy pentamers\textsuperscript{12,13} before development of the one-pot method.\textsuperscript{14–16} To date, the one-pot method has not been applied to the fluoropentamers. A one-pot synthesis for the fluoropentamer 3 was achieved beginning with 2-fluoro-3-nitrobenzoic acid (13), Pd/C-catalysed hydrogenation to 3-amino-2-fluorobenzoic acid 14,\textsuperscript{14,16} and cyclised under the same conditions applied for the methoxy pentamers, using POCl\textsubscript{3} and Et\textsubscript{3}N in dry acetonitrile (Scheme 2).\textsuperscript{14–16} The crude product was purified by sequential washing with dichloromethane, DMF and methanol to give pure 3 as a white powder, albeit in a low yield (4.0%). Washing with DMF was necessary to remove other oligomeric by-products but this step also resulted in some loss of the desired product. The NMR and ESI-MS data for 3 corresponded to that reported in the literature for the same product prepared by the stepwise chain growth method.\textsuperscript{14,15}

\section*{Conclusions}

A macrocyclic pentamer with internal methoxy groups and peripheral benzyloxy groups (1) was prepared via a one-pot synthesis, and the preparation and characterisation of this new pentamer and the benzyloxy-substituted precursors are described. Removal of the benzy group using boron tribromide gave the hydroxy pentamer (2) which can potentially be used to explore further functionalisation for use as a pentagonal building block. A new one-pot synthesis for the macrocyclic pentamer with internal fluoro groups (3) under the standard condition was successfully achieved.

\section*{Experimental section}

\subsection*{General}

All reagents and solvents were obtained from commercial suppliers and used as received unless otherwise noted. All dry solvents were collected from a solvent purifier manufactured by LC Technology Solutions Inc. (http://www.itechline.com). "MilliQ" water was used in all synthetic procedures and HPLC. The LC separations were performed using a DIONEX UltiMate 300 HPG-3400RS pump, a WPS-3000 autosampler, a TCC-3000 column oven, a DAD-3000RS UV lamp and 3000RS Diode Array Detector. An INERT Sustain\textsuperscript{®} UHPLC C18 column (2.1 x 250 mm ID, particle size 3 µm; GL Sciences Inc. Japan) was also employed. An injection volume of 30 µL and a column oven temperature of 25 °C were also employed. The UV detector was operated at 254 nm and 300 nm. High resolution mass spectra were recorded on a Bruker microHCTOFQ (Hybrid Quadrupole Time of Flight) mass spectrophotometer in electrospray ionisation (ESI) mode. For presentation, acquired ESI mass spectra underwent smoothing and baseline subtraction using mMass (Version 5.5.0). The UV/vis absorption measurements were obtained using a Shimadzu UV-vis-NIR spectrophotometer UV-3600 Plus and the software package UVProbe 2.50. Infrared spectra were recorded on a Perkin Elmer Spectrum 100 infrared spectrophotometer. \textsuperscript{1}H, \textsuperscript{13}C NMR, COSY, HSQC, and HMBC spectra were recorded on Bruker Avance III 300, 400 or HD 500 spectrometers. Spectra recorded in CDCl\textsubscript{3} and DMSO-\textsubscript{d}\textsubscript{6} were referenced to the respective residual solvent peaks.

\textbf{Methyl-5-(benzylloxy)-2-hydroxy-3-nitrobenzoic acid, 8}

A mixture of methyl-5-(benzylloxy)-2-hydroxy-3-nitrobenzoate, 7 (0.31 g, 1.2 mmol), Montmorillonite K 10 (0.60 g) and bismuth nitrate (0.47 g, 1.2 mmol) in THF (20 mL) was stirred at r.t. for 1 h. After filtration, the filtrate was evaporated under vacuum, redissolved in CH\textsubscript{2}Cl\textsubscript{2} (150 mL), washed with 1 M HCl and water, dried over Na\textsubscript{2}SO\textsubscript{4} and the solvent removed under vacuum to give a yellow oil which was recrystallised from ice-cold MeOH. Yield: 0.11 g, 31%. HRMS (ESI) [M + H]\textsuperscript{+} = \textsuperscript{calcd} 340.0821 m/z, found 340.0818 m/z, [M + Na]\textsuperscript{+} = \textsuperscript{calcd} 356.0536 m/z, found 356.0534 m/z, [M + K]\textsuperscript{+} = \textsuperscript{calcd} 342.0380 m/z, found 342.0371 m/z. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}); \textit{J} = 11.48 (s, 1H), 7.81 (d, 1H, J = 3.3 Hz), 7.78 (d, 1H, J = 3.3 Hz), 7.41–7.35 (m, 5H), 5.07 (s, 2H), 3.99 (s, 3H). \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}); \textit{J} = 5.07 (s, 2H), 3.99 (s, 3H). Infrared spectra were recorded on Bruker microHCTOFQ (Hybrid Quadrupole Time of Flight) mass spectrophotometer in electrospray ionisation (ESI) mode. For presentation, acquired ESI mass spectra underwent smoothing and baseline subtraction using mMass (Version 5.5.0). The UV/vis absorption measurements were obtained using a Shimadzu UV-vis-NIR spectrophotometer UV-3600 Plus and the software package UVProbe 2.50. Infrared spectra were recorded on a Perkin Elmer Spectrum 100 infrared spectrophotometer. \textsuperscript{1}H, \textsuperscript{13}C NMR, COSY, HSQC, and HMBC spectra were recorded on Bruker Avance III 300, 400 or HD 500 spectrometers. Spectra recorded in CDCl\textsubscript{3} and DMSO-\textsubscript{d}\textsubscript{6} were referenced to the respective residual solvent peaks. Compounds 6,\textsuperscript{26,27} 7 \textsuperscript{14,15} and 14 \textsuperscript{14} were synthesised using reported procedures.

\textbf{Methyl-5-(benzylloxy)-2-methoxy-3-nitrobenzoic acid, 9}

Methyl iodide (0.05 mL, 0.81 mmol) was added to a solution of methyl-5-(benzylloxy)-2-hydroxy-3-nitrobenzoate, 8 (0.07 g, 0.23 mmol) and K\textsubscript{2}CO\textsubscript{3} (0.13 g, 0.92 mmol) in DMF (2 mL). The reaction mixture was heated at 50 °C overnight, the solvent removed under vacuum, redissolved in CH\textsubscript{2}Cl\textsubscript{2} (20 mL), washed with water, dried over MgSO\textsubscript{4} and the solvent removed under vacuum to give a dark-brown oil. Yield: 0.07 g, 99%. HRMS (ESI) [M + H]\textsuperscript{+} = \textsuperscript{calcd} 318.0978 m/z, found 318.0956 m/z, [M + Na]\textsuperscript{+} = \textsuperscript{calcd} 334.0797 m/z, found 334.0781 m/z, [M + K]\textsuperscript{+} = \textsuperscript{calcd} 356.0536 m/z, found 356.0520 m/z. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}); \textit{J} = 7.65 (d, 1H, J = 3.2 Hz), 7.52 (d, 1H, J = 3.2 Hz), 7.42–7.35 (m, 5H), 5.09 (s, 2H), 3.95 (s, 3H). \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}); \textit{J} = 164.49, 153.73, 145.81, 145.59, 135.38, 128.69, 128.42, 128.01, 127.52, 121.86, 114.38, 70.97, 64.24, 52.72.

\textbf{5-(Benzylloxy)-2-methoxy-3-nitrobenzoic acid, 10}

Methyl-5-(benzylloxy)-2-methoxy-3-nitrobenzoate, 9 (0.07 g, 0.23 mmol) was completely dissolved in hot MeOH (4.0 mL). 2
equivalents of 1 M NaOH was added to the solution. The reaction mixture was refluxed for 2 h, the solvent removed under vacuum, quenched with water and neutralised by addition of 1 M HCl until the pH reached 1. A white solid precipitated. The crude product was filtered, washed with water and the solvent removed under vacuum. The creamy yellow precipitate as a crude product was used for the further reaction without purification. Yield: 0.069 g, 99%. HRMS [ESI] [M + Na]⁺ = calc 326.0621 m/z, found 326.0626 m/z. ¹H NMR (300 MHz, CDCl₃): δ = 7.88 (d, 1H, J = 3.2 Hz), 7.64 (d, 1H, J = 3.2 Hz), 7.43–7.35 (m, 5H), 5.13 (s, 2H), 4.02 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ = 166.45, 154.40, 145.16, 135.25, 129.00, 128.79, 127.75, 126.07, 122.76, 116.71, 71.33, 64.94.

3-Amino-5-hydroxy-2-methoxybenzoic acid, 11
A mixture of 5-(benzyloxy)-2-methoxy-3-nitrobenzoic acid, 10 (0.60 g, 2.0 mmol) and Pd/C (0.06 g, 10% in mass) in MeOH (30 mL) was added into a hydrogenation vessel and the nitro group was reduced at 40 C and 450 kPa for 18 h. Filtration and removal of the solvent gave a brown sticky oil product. Yield: 0.348 g, 96%. HRMS [ESI] [M + Na]⁺ = calc 296.0885 m/z, found 296.0899 m/z. ¹H NMR (128 MHz, DMSO-D₆): δ = 10.21 (s, 5H), 8.40 (t, 5H, J = 1.5 Hz), 7.65 (t, 5H, J = 1.5 Hz), 7.44 (t, 5H, J = 7.8 Hz).

3-Amino-5-(benzyloxy)-2-methoxybenzoic acid, 12
A mixture of 5-(benzyloxy)-2-methoxy-3-nitrobenzoic acid, 10 (0.70 g, 2.3 mmol) and Pu/C (0.07 g, 10% in mass) in MeOH (80 mL) was added into a hydrogenation vessel and the nitro group was reduced at 40 °C and 450 kPa for 18 h. Filtration and removal of the solvent gave a brown sticky oil product. Yield: 0.605 g, 97%. HRMS [ESI] [M + H]⁺ = calc 274.1079 m/z, found 274.1068 m/z, [M + Na]⁺ = calc 296.0899 m/z, found 296.0885 m/z. ¹H NMR (300 MHz, CDCl₃): δ = 7.40–7.37 (m, 5H), 7.08 (d, 1H, J = 2.8 Hz), 6.06 (d, 1H, J = 2.8 Hz), 5.02 (s, 2H), 3.88 (s, 3H). ¹³C NMR (128 MHz, DMSO-d₆): δ = 153.15, 142.99, 138.47, 125.81, 104.83, 103.48, 60.07. UV-vis (λ_max/nm (ε/M⁻¹ cm⁻¹), DMSO): 330 (4112), 267 (3912).

Pentahydroxypentamer, 2
Boron tribromide (0.008 mL, 0.078 mmol) was added to a solution of pentahydroxypentamer, 1 (10 mg, 0.008 mmol) in dry CH₂Cl₂ (20.0 mL) at 0 °C. The mixture was stirred at r.t. overnight under N₂ atmosphere. The solution was decanted off. The remaining solid was washed with water, the solvent removed under vacuum, re-dissolved in MeOH (20 mL) and a small portion of the crude product was purified by analytical RP-HPLC (eluted with 100% water for 5 min and 0–100% linear increase of MeOH for 25 min at a maintained flow rate of 1 mL min⁻¹) to give a white solid. Yield: 1.9 mg, 29%. HRMS [ESI] [M + Na]⁺ = calc 848.2027 m/z, found 848.2013 m/z.

Fluoropentamer, 3
POCl₃ (0.21 mL, 2.2 mmol) was added to a solution of 3-amino-2-fluorobenzoic acid, 14 (0.17 g, 1.1 mmol) in dry MeCN (10 mL) at r.t. The mixture was stirred vigorously for 10 min. Et₃N (0.44 mL, 3.3 mmol) was added to the reaction mixture which was stirred overnight at r.t. After removal of the solvent, the residue was washed with CH₂Cl₂ (50 mL × 2), MeOH (50 mL) and DMF (20 mL) to give an off-white solid. Yield: 7.0 mg, 4.0%. HRMS [ESI] [M + Na]⁺ = calc 708.1282 m/z, found 708.1303 m/z. ¹H NMR (400 MHz, DMSO-d₆): δ = 10.21 (s, 5H), 8.40 (t, 5H, J = 1.5 Hz), 7.65 (t, 5H, J = 1.5 Hz), 7.44 (t, 5H, J = 7.8 Hz).

Conflicts of interest
There are no conflicts to declare.

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Yield was estimated based on a proportion of the product peak (which came first) relative to the other peaks of by-products which are the corresponding de-methylated macrocycles of internal methyl groups in the HPLC chromatogram at 254 nm.