Microwave-assisted synthesis of a new series of resorcin[4]arene cavitand-capped porphyrin capsules†

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Capsule-shaped molecular receptors are fundamental to the modeling of biological host–guest interactions such as those characteristic of enzymatic processes. Among the more versatile and effective synthetic receptors are the hemicarcerand-type hosts. Herein we report the synthesis of six novel resorcin[4]arene cavitand-capped porphyrin capsules, in a new series of molecular capsules modeled on the classical hemicarcerands initially reported by Cram and co-workers. In the first reported instance of its utilisation in the preparation of supramolecularly-capped porphyrin host molecules, microwave (MW) irradiation was used (in conjunction with Adler conditions) in order to form the porphyrin cap *in situ*. Additionally, the yields obtained *via* these conditions exhibited a significant improvement, relative to the traditional refluxing protocol hitherto reported. Capsules **20–25** are indefinitely stable, and we observed that **22** and **25** possess the smallest rigidified cavities yet reported for resorcin[4]arene cavitand-capped porphyrin host molecules.

Introduction

Biological enzymes function selectively with respect to the chemical reactions that they facilitate.[1–4] The shape- and size-specificity which they exhibit stem largely from the molecular recognition and binding of substrates. One of the major themes within bioorganic chemistry is the design of simpler, synthetic complexes and molecules that are able to mimic the enzymatic active sites responsible for these substrate recognition events, and subsequent enzymatic processes.[5,6] Indeed, the recognition and selectivity which a receptor exhibits towards guest size and shape, and the ability of the receptor to retain within (and release from) the confines of the molecular cavity are vital aspects which need to be considered in the design of such host–guest systems.[7]

Synthetic molecular recognition modeling in chemistry has yielded a wide variety of cavity-containing host molecules, capable of binding a range of guest molecules.[6,8–10] These receptors can be divided into two general categories: carcerand-like, and hemicarcerand-like species.

The former consists of rigid, covalently bonded capsule-like molecules which are able to interact strongly with guests such that they are incarcerated indefinitely within the confines of the host cavity. The latter consists of more flexible, covalently bonded capsules, where guests are reversibly bound within the confines of the host molecule in a more selective manner.[6,11–17]

In the modeling of the active sites of biological catalysts, therefore, hemicarcerand-type receptors are of particular importance, as a means of mimicking substrate recognition and reversible binding, both of which are characteristic of enzymes.

As active-site analogues of heme-based enzymes, synthetic porphyrins and their metalloporphyrins derivatives are widely used in supramolecular chemistry in order to model a number of biologically important metallo-enzymes, most notably the cytochrome monooxygenases.[4,18,19] Additionally, these macrocycles have been incorporated into a number of hemicarcerand-type receptor molecules, where the presence of the hydrophobic cavity has been shown to enhance guest binding and the coordination of ligands to the porphyrinic metal centre.[20] Such bridged or capped superstructured porphyrins have made use of receptors such as crown ethers,[21–24] cyclodextrins,[25–27] calix[4]arenes,[5,24] and, as in the focus of this study, resorcin[4]arene cavitands.[15,28–30]

Resorcin[4]arene cavitands posses a rigid and well defined cavity, and as such have been observed to significantly enhance the binding and encapsulating abilities of capped porphyrin receptor molecules. In the first reported example of resocin[4]arene cavitand-capped porphyrins, Reinhoudt and co-workers synthesised a number of receptors bearing di- and tetraamide bridges (comprising five or nine atoms) capable of enhanced coordination of *N*-heterocycles.[28] The receptors, in particular the highly rigidified analogues, exhibited up to a 700-fold enhancement in binding (relative to simple tetraphenylporphyrin (TPP) analogues) in the case of some guests.[28] However, the use of amide bridges induced a degree of ligand instability. In a different approach, Naruta and co-workers have published (several) reports pertaining to the synthesis and binding capabilities of a hemicarcerand-type resorcin[4]arene cavitand-capped porphyrin.[29,30] The use of two short, adjacent ether bridges (two atoms in length), in the construction of a 'pac-man' kind of ligand,[31] allows the reversible encapsulation of various hydrocarbons with noteworthy guest exchange rates.[15,29,30]

Classical hemicarcerands, as pioneered by Cram and co-workers, are well documented as receptors to a vast range and number of guest molecules.[32–35] Fundamentally, complexation investigations of the reported hosts indicated that the shape and size of the portals governing access to the molecular cavity were of particular importance in the binding abilities of the receptor

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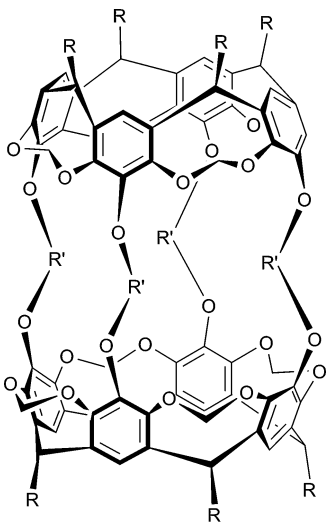
molecule. This phenomenon was reported by Reinhoudt and Naruta in the case of resorcin[4]arene-capped porphyrin receptors.

Among the "strongest and most versatile hemicarcerand yet prepared", is that reported by Robbins *et al.*,[17] which was able to (reversibly) form 30 various hemicarceplexes with a number of aliphatic and aromatic guests. The hemicarcerand prepared made use of ether bridges, in which the two hemispheres of the receptor were interconnected by four -$O(CH_2)_4O$- bridges (Fig. 1). Given the versatility of the reported hemicarcerand, our capsule design aimed at the inclusion of -$O(CH_2)_4O$- bridges in the synthesis of a new series of porphyrin-hemicarcerand-type receptor molecules. Coupling the ligating properties of the porphyrin macrocycle with the versatility of the ether bridges has the promise to yield a receptor ligand with potentially unique, and thus valuable binding properties in the study of biomimetic catalysts. However, given the importance of size and shape of the molecular portals in determining the binding characteristics of container molecules, we chose to synthesise a range of molecules.



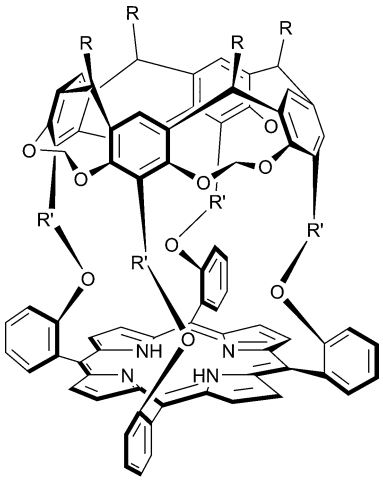
R = C_5H_{11}, $CH_2CH_2C_6H_5$
R' = $(CH_2)_4$

Fig. 1 Schematic representation of the classical hemicarcerand host reported by Robbins *et al.*, reported as being among the most versatile hosts prepared.

In this paper, we thus describe the successful synthesis of new resorcin[4]arene cavitand-capped porphyrin capsules, bearing four ether bridges (Fig. 2). The synthesis, with the use of hitherto unreported microwave (MW) techniques, has resulted in a series of stable, completely rigidified receptor molecules. We determine that these capsules are among those having the smallest *rigidified* cavity reported for hemicarcerand-type compounds. Indeed, the use of the ether bridges employed yields receptors corresponding to the classical hemicarcerand receptors investigated by Cram and co-workers.[14,16,17,36–38]

Results and discussion

The success of Naruta in the preparation of ether-bridged capped-porphyrin receptors capable of effective binding of guest molecules prompted us to commence our synthesis with the implementation



R = CH_3, C_5H_{11}, $CH_2CH_2C_6H_5$
R' = $O(CH_2)_4$, $O(CH_2)_3$, $O(CH_2)_2$, CH_2

Fig. 2 The general structure of the capped porphyrin target capsules investigated in this report.

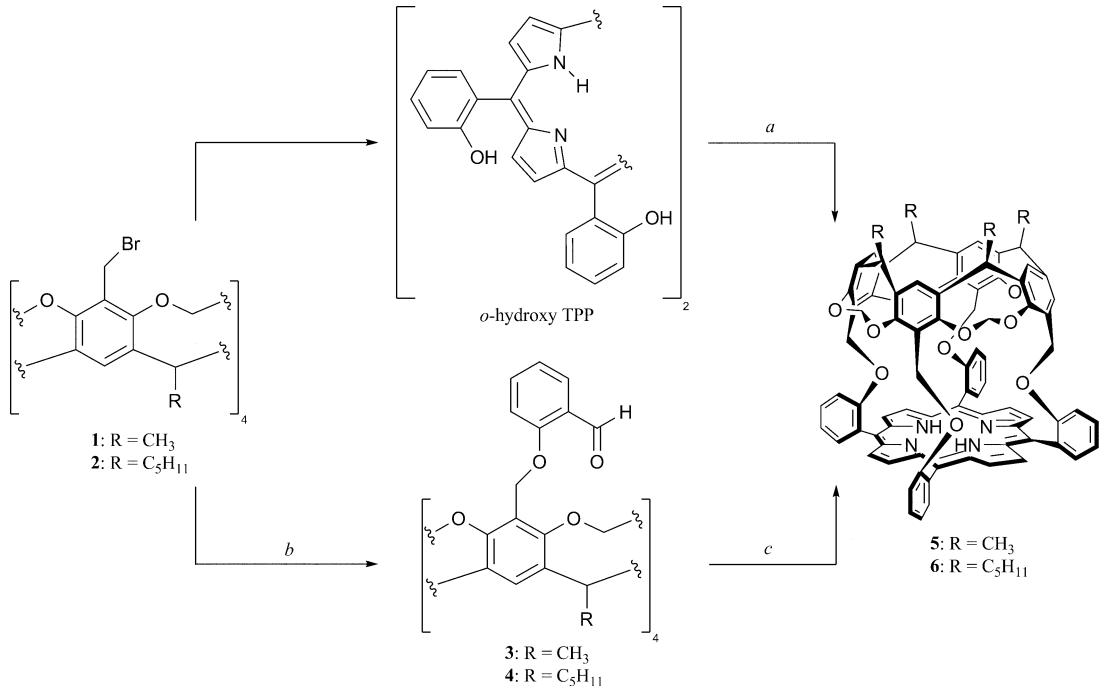
of short, two-atom (-CH_2O-) bridges according to Scheme 1. Resorcin[4]arene cavitands **1** and **2**[39,40] were initially reacted (in a stoichiometric amount) with *o*-hydroxy TPP (top, Scheme 1) under conditions identical to those cited by Naruta and co-workers, in the synthesis of their ligands. This approach failed to yield the desired synthetic targets, despite a number of changes to protocol.[41]

In light of the failed synthesis, the protocol adopted by Reinhoudt and co-workers was used (bottom, Scheme 1). Thus, **1** and **2** were reacted with salicylaldehyde in the presence of NaH and THF to give the novel aldehydes **3** and **4**. This resulted in the incorporation of the aromatic aldehyde, required for cyclisation and porphyrin formation, into the resorcin[4]arene cavitand scaffold. The synthesis of **5** and **6** was subsequently attempted, with the addition of pyrrole, using the Adler conditions.[42]

In a synthetic protocol identical to that adopted by Reinhoudt, aldehyde **3** was dissolved in propionic acid (200 mL), and brought to reflux under atmospheric conditions, at which time freshly distilled pyrrole was added to the solution. The reaction vessel was shielded from light, and reflux continued for 30 minutes. Thereafter, the solution was allowed to cool to ambient temperature and stir overnight. UV-Vis analysis of an aliquot of reaction solution on working up the reaction mixture, however, failed to confirm the presence of porphyrinic material by the absence of the intense Soret band, associated with porphyrins, at 419 nm. A similar result was observed when aldehyde precursor **4** was used towards the synthesis of **6**.

Single-crystal X-ray crystallographic analysis of precursor **3** offers a potential explanation as to why target **5** bearing short bridges could not be prepared in this manner. Figs. 3 and 4 show the ORTEP diagram of aldehyde **3**.[43] The relative orientations of the salicylaldehyde residues are clearly evident: two are present as upright while the remaining two are found to be splayed, facing away from the molecular cavity.

This orientation is indicative of a noticeable degree of steric crowding above the resorcinarene cavity, which creates insufficient space to accommodate the salicylaldehyde residues in a symmetric



Scheme 1 Proposed synthetic pathways towards the initial synthetic targets. *Reagents and conditions*: *a*) K_2CO_3, NMP, THF, 120 °C, 4 days; *b*) NaH, THF, salicylaldehyde, reflux; *c*) pyrrole, propionic acid, reflux, 30 min.

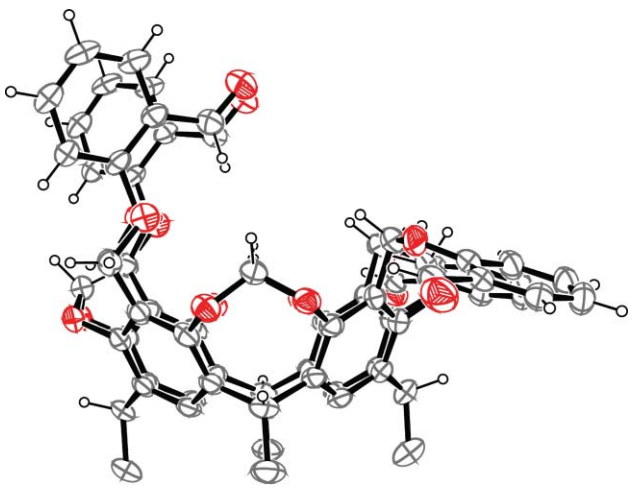


Fig. 3 The ORTEP diagram of **3**, shown side-on. Ellipsoids are shown at the 30% probability level, with the hydrogen atoms (where shown) appearing as spheres of arbitrary radii.

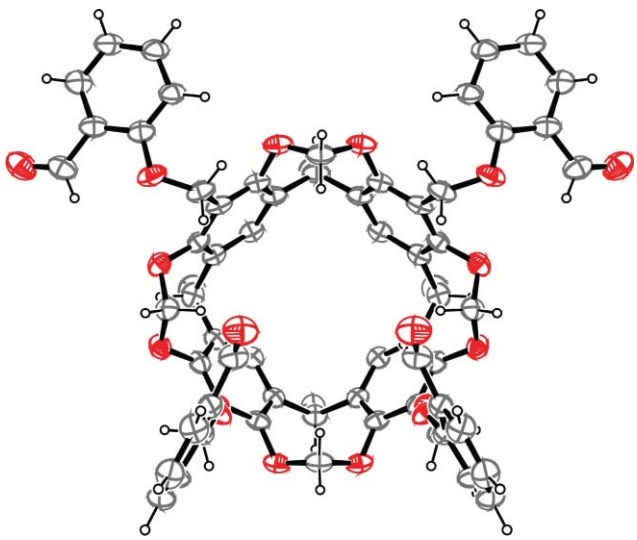
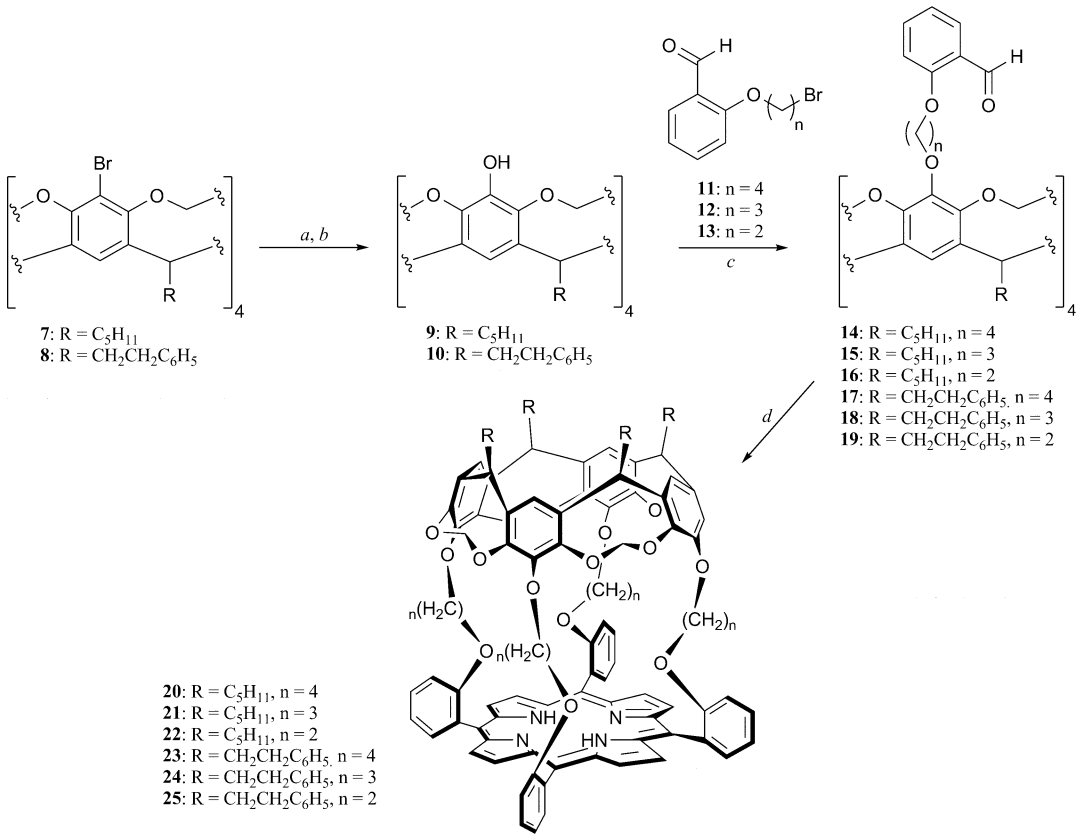


Fig. 4 The ORTEP diagram of **3**, shown from above the molecular cavity. Ellipsoids and hydrogen atoms appear as described in Fig. 3.

manner. During cyclisation, therefore, while a number of the salicylaldehyde residues may indeed react with a corresponding pyrrole unit, the accommodation of the remaining pyrrole units may not be possible in a manner free of significant strain, leading to incomplete cyclisation. Fundamentally, however, the short nature of the -CH_2O- unit prevents capsule synthesis, and infers the presence of a *minimum* bridge length requirement in order to give a successful synthesis of resorcin[4]arene cavitand-capped porphyrins.

Design of larger capsules

Given that the synthesis failed, and bearing in mind the ultimate aim of including -$O(CH_2)_4O$- bridges into our receptors, the synthesis was redesigned towards the inclusion of longer bridges. The series of capped porphyrins was synthesised starting from resorcin[4]arene cavitands **7** and **8** (Scheme 2), which were prepared from the corresponding resorcin[4]arenes according to procedures in literature, in 69% and 70% yields respectively.[12,44,45] These were lithiated according to the literature procedure to produce pure



Scheme 2 Redesigned synthetic pathway towards target capped porphyrin receptors. *Reagents and conditions*: *a*) THF, *n*-BuLi, $B(OCH_3)_3$, −78 °C; *b*) 15% H_2O_2/1.5 M NaOH (1:1); *c*) K_2CO_3, DMF, 55 °C; *d*) pyrrole, propionic acid.

tetrols **9** and **10**, in respective yields of 40% and 45%.[46] In order to synthesise the capped porphyrins, the required aromatic aldehyde was incorporated into the resorcin[4]arene cavitand scaffold. As such, a series of aldehyde reagents were synthesised from salicylaldehyde and various dibromoalkanes. Thus 1,4-dibromobutane, 1,3-dibromopropane, and 1,2-dibromoethane were reacted with salicylaldehyde in the presence of K_2CO_3 and DMF to produce aldehydes **11**, **12** and **13**, respectively.[47] A series of six novel aldehyde resorcin[4]arene cavitands were subsequently prepared by reaction of tetrols **9** and **10** with aldehyde reagents **11**, **12** and **13**, in DMF in the presence of K_2CO_3. The six new aldehydes **14–19** were prepared in reasonable yields (70–90%).

In order to augment the Adler cyclisation conditions, we turned to MW energy as a means of enhancing reaction conditions towards improving our yields of receptor target molecules. MW heating has been shown to increase reaction rates of organic reactions by rapidly heating at a molecular level.[48,49] It has become increasingly popular as a means by which to synthesise *meso*-tetraphenylporphyrin derivatives and their corresponding metalloporphyrins,[50–55] where the production of a porphyrin from pyrrole and an aromatic aldehyde is determined largely by kinetic factors.[56–58] De Paula *et al.*[55] have recently investigated the kinetics of the Adler synthesis of *meso*-TPP under MW irradiation. Using the cited reaction conditions as a basis, the synthesis of **20–25** was attempted using MW-assisted techniques. Thus, **14** was dissolved in a small amount of propionic acid, and heated using MW irradiation in the presence of four equivalents of pyrrole. After stirring overnight in air, and subsequent extraction, UV-Vis analysis of an aliquot of reaction solution confirmed the presence of porphyrinic material by the intense Soret band, at 419 nm.

A series of reactions followed in order to optimise synthetic conditions. This included varying reaction times, temperatures, and reagent concentration.[59] It was subsequently found that reactions performed at 160 °C for five minutes, using a reactant concentration of 0.01 mol dm^{-3} gave an average yield of 10% after purification. This represents the first reported instance of the use of MW irradiation in the synthesis of porphyrins capped with supramolceular moeities (including resorcin[4]arenes, resorcin[4]arene cavitands, calixarenes, cyclodextrins and crown ethers). Interestingly, longer reaction times of 20 minutes at 160 °C gave poorer yields, as did slightly shorter reaction times of three minutes. Reactions performed at 145 °C (similar to the temperatures used in the Adler reflux) also gave diminished yields, while heating at 180 °C had no significant effect on reaction yield. Reactions performed at temperatures below the boiling point of propionic acid (120 °C) did not yield any porphyrinic material. Additionally, any changes in reagent concentration had a negligible influence on yield obtained.[60] The presence of capped porphyrin **20** was readily identified with the use of ^{1}H NMR spectroscopy, by the presence of an upfield signal resonating at δ −2.8 as a result of the two amine protons found at the core of the porphyrin free base. The presence of the parent molecular ion peak in subsequent positive high resolution ESI-TOF mass spectrometry served to further confirm the successful synthesis of **20**. Additionally, the microcrystalline material obtained was indefinitely stable, in contrast to the ligands reported by Reinhoudt.

Table 1 Reaction yields of the series of capsules prepared by the Adler conditions under MW conditions

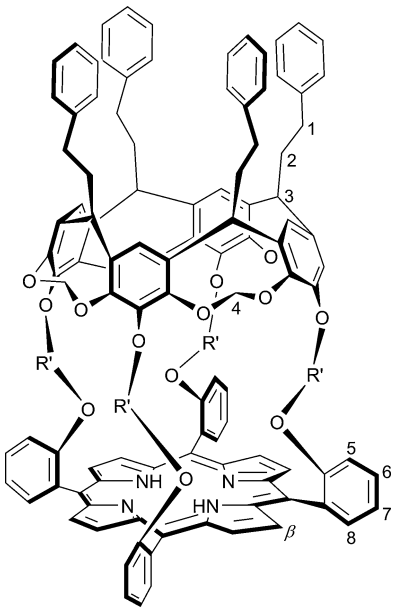
Molecule	Yield (%)
20	10
21	10
22	17
23	8
24	13
25	18

The remaining capsules were consequently synthesised using the optimised MW-assisted method used in the preparation of **20**, as summarised in Table 1. The results indicate a notable increase in reaction yield as the length of interconnecting bridge decreases.

NMR analysis

Structural proof for the novel resorcin[4]arene cavitand-porphyrin receptor molecules was obtained by the use of 1D and 2D NMR spectroscopy. The ^{1}H NMR spectra of **23–25** are presented in the annotated Fig. 5, with reference to Fig. 6 indicating the assignment of common signals present in all three receptors discussed. COSY and ^{13}C spectra are presented as part of the ESI†.

The ^{1}H NMR spectrum of **25** (i, Fig. 5) clearly shows the presence of the porphyrinic amine protons at an upfield position of δ −2.88, serving as confirmation of the synthesis of the porphyrin macrocycle. The spectrum also illustrates the inherent symmetry (C_4) of the molecular structure. This is in contrast to the receptors reported by Reinhoudt,[28] where rotamers were observed by NMR techniques. The two methylene groups found in the interconnecting bridges are easily distinguished from each other by the upfield shift of the OCH_2 methylene group closest to the porphyrin



25 : R' = -CH_2CH_2-
24 : R' = -$CH_2CH_2CH_2$-
23 : R' = -$CH_2CH_2CH_2CH_2$-

Fig. 6 Schematic representation of capsules **23–25**, indicating the protons responsible for the signals observed in Fig. 5. For clarity, those protons common to all three receptors are shown.

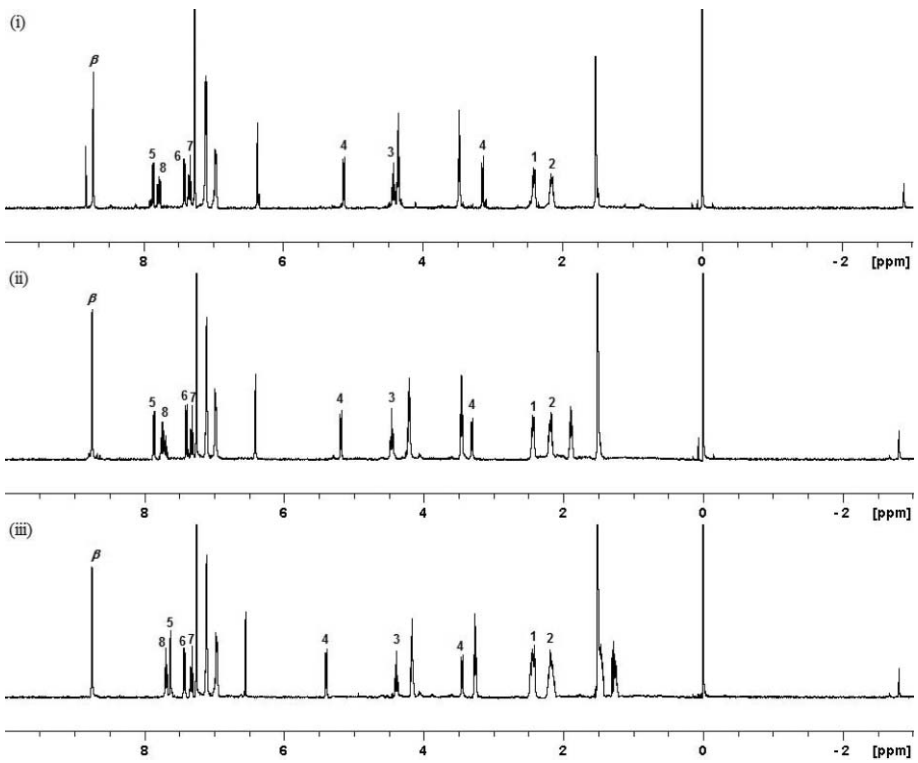


Fig. 5 The ^{1}H NMR spectra of **23–25** from −3.0 ppm to 10.0 ppm. For discussion purposes, spectrum (i) refers to **25**, (ii) to **24**, and (iii) to **23**. Me_4Si was used in each case as an internal standard. Signal annotations are made with reference to Fig. 6.

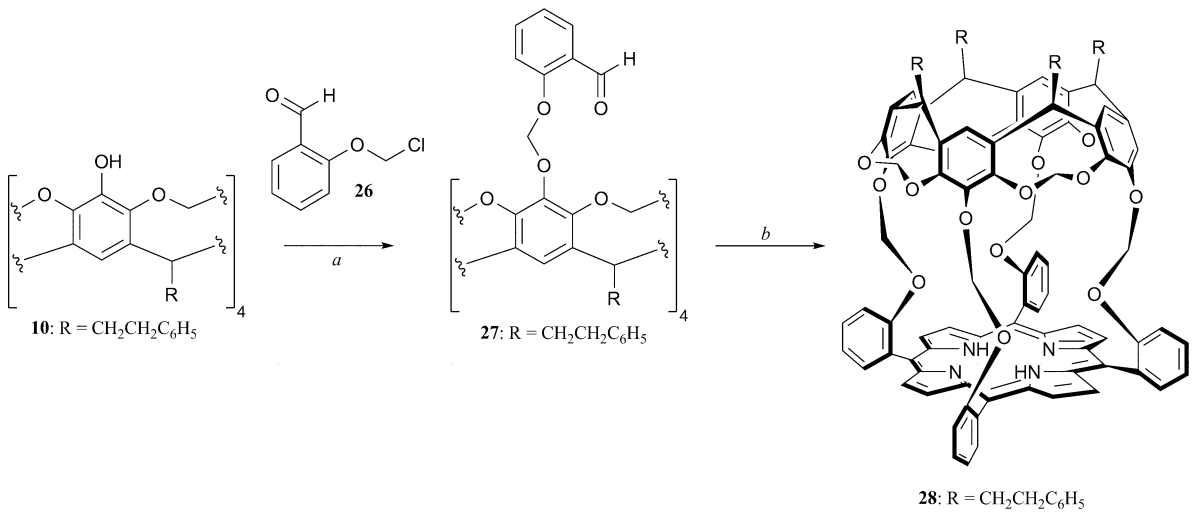
macrocycle. The influence of the porphyrinic ring current has shifted the signal for this methylene group approximately 1.0 ppm upfield (to δ 3.48) relative to the remaining OCH_2 methylene group (δ 4.42). The anisotropy of the resorcin[4]arene cavitand OCH_2O intramolecular bridges (proton 4, Figs. 5 and 6) has also been influenced by the capsule-like nature of the receptor. The 'outer' proton has shifted approximately 0.5 ppm upfield to δ 5.12, while the 'inner' proton has experienced an upfield shift of 1.0 ppm, resonating at δ 3.14. The signals related to the *meso*-phenyl rings of the porphyrin exhibit multiplets at δ 7.31, 7.42, 7.77 and 7.85 (protons 7, 6, 8 and 5, respectively, in Figs. 5 and 6), all of which integrate to four protons (see ESI for full spectra†). Relative to aldehyde precursor **19**, there has been a slight upfield shift in the chemical shifts of these protons, due to the presence of the porphyrin ring current. The β-pyrrole protons of the porphyrin moiety resonate as a pair of singlets at δ 8.82 and 8.71, having relative intensities of approximately 2:1.

The ^{1}H NMR spectrum of **24** (ii, Fig. 5) appears very similar to that of **25**, as anticipated. The presence of the upfield porphyrinic amine protons at δ –2.82 is again evident. The presence of the extra methylene group (compared to **25**) in the bridges results in an additional signal at δ 1.87, while the neighbouring OCH_2 methylene groups again resonate at δ 3.44 and 4.19, at similar chemical shifts observed in the case of **25**. The β-pyrrole protons in the case of **24** give rise to a singlet at δ 8.73. The remainder of the spectrum exhibits almost identical signal chemical shifts, relative to those seen in **25**, as illustrated in Fig. 5.

The ^{1}H NMR spectrum (iii, Fig. 5) of the third capsule in the series, **23**, again appears similar to those of **25** and **24**. Once again the porphyrinic amine protons can be seen resonating at δ –2.81. However, differences appear in the position of a number of signals due to the increased distance between the porphyrin and resorcin[4]arene moieties. The aromatic signals for the *meso*-phenyl rings of the porphyrin exhibit notable shifts, with the signal due to proton 5 (Fig. 6) shifting upfield to δ 7.63. In comparison to **24** and **25**, protons 5 and 8 have thus swapped relative positions, with proton 8 remaining at approximately δ 7.72. The elongated nature of the capsule in **23** has also decreased the related shielding effect on a number of protons forming part of the resorcin[4]arene cavitand scaffold. The signal for the 'outer' resorcin[4]arene cavitand OCH_2O protons now resonates at δ 5.40, representing a downfield shift of 0.3 ppm relative to the corresponding signal in the case of **24** and **25**. In addition, the 'inner' protons (proton 4) are now observed to resonate at a position downfield (δ 3.46) in relation to the triplet (δ 3.23) belonging to the methylene group forming part of the $-O(CH_2)_4-$ bridges. This is in contrast to the relative arrangement for these signals observed in **24** and **25**, illustrated more clearly in Fig. 5. Finally, the introduction of an additional methylene group into the interconnecting bridges results in a signal resonating in the alkyl region as a multiplet at δ 1.30. The neighbouring methylene group, previously resonating at δ 1.87, has experienced an upfield shift to resonate at δ 1.49. The assignment of these two signals in particular was further aided by the use of a COSY spectrum. Thus, the signal resonating at the upfield position (δ 1.30) is a result of the $-O(CH_2)_2CH_2CH_2O-$ methylene group found closest to the porphyrin ring current.

Identification of minimum bridge length

Having successfully prepared capsules bearing six-, five- and four-atom bridges, synthesis towards the preparation of the three-atom bridged analogue was undertaken. This was to establish the minimum bridge length which afforded a successful synthesis for this class of capped porphyrin; a phenomenon that was inferred by the observations in the attempted preparation of **5**. The preparation protocol (Scheme 3) made use of precursor **10**, in a synthesis very similar to that which afforded **20**–**25**. Thus, **10** was reacted with aldehyde **26**[61] to give resorcin[4]arene cavitand **27**. The MW-assisted cyclisation conditions cited above were subsequently used on this precursor to synthesise **28**. However, preliminary UV-Vis analysis of the reaction product indicated the absence of the characteristic Soret band indicative of porphyrin formation. This result thus indicates that, with regards to our series



Scheme 3 Proposed synthetic protocol towards three-atom bridged receptors. *Reagents and conditions*: *a*) NaH, THF, reflux; *b*) pyrrole, propionic acid, MW 160 °C, 5 min.

of capped porphyrin receptors, the minimum requirement of bridge length to successfully obtain a capped porphyrin is four atoms.

Capsule synthesis using conventional heating

Our final synthetic investigation involved examining the efficacy of the Adler reflux conditions in the synthesis of our series of capsules. For comparative purposes, and indeed, given the yields obtained *via* the MW-assisted technique, the synthesis of receptors **21**, **22**, **24** and **25** was attempted using conditions identical to those employed in the attempted synthesis of **5** and **6**. In all four cases, UV-Vis analysis of reaction aliquots after extraction exhibited the presence of the Soret band at 419 nm; an indication that the series of reactions was successful. In the case of **22** and **25**, purification and recrystallisation gave receptors which were characterised successfully by NMR spectroscopic techniques to confirm their successful synthesis. However, yields were diminished (as anticipated), amounting to approximately half those (10–11%) observed in Table 1 for the respective capsules. In the case of **21** and **24**, the value of the MW-assisted method was highlighted. Although UV-Vis and preliminary ^{1}H NMR spectroscopy confirmed that the classical reflux protocol afforded both capsules, the material could not be completely separated from the reaction matrix by column chromatography, despite a number of alterations to chromatographic conditions. Hence, receptors **21** and **24** could not be obtained as analytically pure on application of the reflux methodology. This is in contrast to the MW-assisted technique, where both capsules were readily purified. Indeed, cleaner reaction profiles are characteristic of organic MW reactions.[62] The added benefit (in all cases) of the MW-assisted technique, besides the very short reaction times, was that significantly less propionic acid was used; 4 mL in the MW reactions, as opposed to 200 mL in the case of the reactions using conventional heating.

Conclusions

An efficient means of preparing a new series of resorcin[4]arene cavitand-capped porphyrin receptor is reported, each bearing an ether-based interconnecting bridge. The use of ether bridges has resulted in enhanced stability, relative to the amide-based bridged system reported previously. Among the prepared capped porphyrins are capsules having the smallest rigidified cavity among known hemicarcerand compounds. Additionally, the synthetic protocol utilised MW techniques (in conjunction with the Adler conditions for porphyrin synthesis), which are hitherto unreported in the synthesis of hemicarcerand-type, supramolecularly capped porphyirn receptor molecules. The use of MW-assisted heating also resulted in significant enhancement in yields of the synthetic targets relative to the classical reflux methodology. Indeed, synthesis was *unable* to yield **21** and **24** analytically pure *without* the use of MW heating, thereby illustrating the value of the technique. Synthetic results also indicated that, with regards to these type of supramolecular porphyrins, a minimum bridge length exists in order to successfully obtain the molecules. The binding abilities of the new series of capsules are currently under investigation.

Experimental

General

All solvents and reagents were obtained from Acros, Aldrich, Fluka, Merck or Alfa-Aesar. Unless otherwise stated, these were used without further purification. Microwave synthesis was completed using a CEM Liberty microwave peptide synthesiser, using sealed borosilicate tubes. Yields for the MW-assisted reaction are reported as average yield *per* reaction. Thin-layer chromatography (TLC) was conducted on aluminium-backed, precoated silica gel plates (Merck, silica gel 60, 20 cm × 20 cm). Column chromatography was performed with silica gel 60 (Merck, particle size 0.040–0.063 mm). Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded using a Bruker Avance spectrometer, operating at ambient temperatures, at 400 MHz for ^{1}H experiments, and 100 MHz for ^{13}C experiments. Chemical shifts are reported in parts per million (ppm). Ultraviolet-Visible spectra were recorded at 298 K on a Varian Cary 50 CONC single beam UV-Vis spectrophotometer, using a quartz cell of 1 cm path length and an analyte concentration of approximately 100 ppm. Infrared (IR) spectra were recorded on a Nicolet Impact 400 spectrophotometer at 293 K, as KBr discs. All melting points are uncorrected. Elemental microanalyses were obtained using a Leco CHNS-932 micro-elemental analyzer. High resolution mass spectrometric data was obtained using a Bruker micrOTOF-Q II instrument operating at ambient temperatures, using a sample concentration of approximately 1 ppm.

7,11,15,28-Tetrakis[(2-formylphenoxy)methylene]-1,21,23,25-tetramethyl-2,20:3,19-dimetheno-1*H*,21*H*,23*H*,25*H*-bis[1,3]dioxocino[5,4-*i*:5′,4′-*i*′]benzo[1,2-*d*:5,4-*d*′]-bis[1,3]benzodioxocin stereoisomer (3). To a stirring solution of salicylaldehyde (1.01 g, 8.30 mmol) in dry THF (70 mL) under a nitrogen atmosphere, NaH (60% suspension in mineral oil, 0.33 g, 8.30 mmol) was added. To the resulting bright yellow solution, tetrabromomethyl cavitand **1** (1.00 g, 1.04 mmol) was added as a solution in dry THF (10 mL), dropwise over 30 minutes. The solution was refluxed for four days; TLC over this period showed mono-, di-, tri- and tetra-substituted products. Over this time, the solution became grey in colour. Once cooled to room temperature, the solution was concentrated *in vacuo*. The products were chromatographed on silica gel using a mobile phase of 3:2 hexane–ethyl acetate. Fractions of 12 mL were collected, combining all fractions containing the desired tetra-substituted product (R_f 0.37) after separation. The purified product concentrated on a rotary evaporator to yield an off-white solid; this was then stirred in methanol overnight. After filtration, the product was collected and stirred overnight in hexane to remove residual aldehyde, before being filtered and collected to yield **3** (0.35 g, 28%) as a white solid (Found: C, 72.5; H, 5.1. $C_{68}H_{56}O_{16}$ requires C, 72.3; H, 5.0%); mp 127–130 °C (from ethyl acetate/hexane). ν_{max}(KBr)/cm^{-1} 2985, 2940, 2870, 1735, 1690, 1600, 1585, 1480, 1465, 1400, 1385, 1340, 1300, 1290, 1240, 1220, 1195, 1165, 1100, 1075, 1020, 975, 940, 850, 835, 755, 670, 645, 585, 500, 445; δ_H(400 MHz, $CDCl_3$) 1.88 (d, *J* 7.6 Hz, 12 H, CH_3), 4.57 (d, *J* 6.9 Hz, 4 H, inner of OCH_2O), 4.96 (s, 8 H, ArOCH_2Ar), 5.05 (q, *J* 7.1 Hz, 4 H, C*H*CH$_3$), 5.82 (d, *J* 6.8 Hz, 4 H, outer of OCH_2O), 7.04 (t, *J* 7.1 Hz, 4 H, Ar *H*), 7.14 (d, *J* 8.5 Hz, 4 H, Ar *H*), 7.40 (s, 4 H, cavitand Ar *H*), 7.53 (t, *J* 7.0 Hz, 4 H, Ar *H*), 7.73 (d, *J* 7.6 Hz, 4 H, Ar *H*), 10.18 (s, 4 H, Ar C*H*O); δ_C(100 MHz,

$CDCl_3$) 189.8, 160.9, 154.0, 139.0, 135.8, 129.7, 125.5, 121.7, 121.4, 114.1, 100.0, 62.0, 31.2, 16.1.

7,11,15,28-Tetrakis[(2-formylphenoxy)methylene]-1,21,23,25-tetrapentyl-2,20:3,19-dimetheno-1*H*,21*H*,23*H*,25*H*-bis[1,3]dioxocino[5,4-*i*:5′,4′-*i*′]benzo[1,2-*d*:5,4-*d*′]-bis[1,3]benzodioxocin stereoisomer (4). Similar procedure as for the preparation of **3**, applied to salicylaldehyde (0.36 g, 2.69 mmol) in dry THF (50 mL) under a nitrogen atmosphere, NaH (60% suspension in mineral oil, 0.065 g, 2.69 mmol), and tetrabromomethyl cavitand **2** (0.40 g, 0.34 mmol). After 3 days of reflux, TLC showed tri- and tetra-substituted products. The products were chromatographed on silica gel using a mobile phase of 1:1 hexane–ethyl acetate. Fractions containing the desired tetra-substituted product (R_f 0.56) were combined, and concentrated *in vacuo* to yield a white solid. The material was then stirred in methanol, before being filtered and collected to yield **4** (0.33 g, 80%) as a white solid (Found: C, 74.8; H, 6.7. $C_{84}H_{88}O_{16}$ requires C, 74.5; H, 6.5%); mp 136–138 °C. ν_{max}(KBr)/cm^{-1} 2929, 2859, 1686, 1597, 1476, 1454, 1378, 1283, 1240, 1189, 1151, 1088, 1019, 964, 853, 755, 654, 585, 487, 441; δ_H(400 MHz, $CDCl_3$) 0.91 (t, *J* 7.1 Hz, 12 H, C*H*$_3$), 1.36 (m, 24 H, (C*H*$_2$)$_3$), 2.26 (m, 8 H, C*H*$_2$), 4.54 (d, *J* 7.1 Hz, 4 H, inner of OC*H*$_2$O), 4.83 (t, *J* 8.1 Hz, 4 H, C*H*(CH$_2$)$_4$CH$_3$), 4.95 (s, 8 H, ArOC*H*$_2$Ar), 5.77 (d, *J* 7.0 Hz, 4 H, outer of OC*H*$_2$O), 7.03 (t, *J* 7.5 Hz, 4 H, Ar *H*), 7.14 (d, *J* 8.4 Hz, 4 H, Ar *H*), 7.27 (s, 4 H, cavitand Ar *H*), 7.53 (td, *J* 8.9 Hz, 4 H, Ar *H*), 7.73 (dd, *J* 7.5 Hz, 4 H, Ar *H*), 10.17 (s, 4 H, Ar C*H*O); δ_C(100 MHz, $CDCl_3$) 189.93, 160.95, 154.44, 138.19, 135.87, 129.70, 125.55, 121.93, 121.41, 114.17, 100.07, 62.11, 36.94, 32.02, 30.12, 27.58, 22.70, 14.13.

General procedure for preparation of tetraaldehyde resorcin[4]arene cavitands 14–19. To a stirring solution of oven-dried (110 °C) K_2CO_3 in dry DMF (40 mL), dry tetrol was added and stirred until completely dissolved. To the resulting light yellow solution, the respective aldehyde reagent was added and the reaction mixture gently heated at 55 °C for three days. During this period, the solution became yellow and cloudy, with a white deposit on the sides of the reaction vessel. The mixture was cooled to room temperature, at which time the unreacted K_2CO_3 and the white precipitate was gravity-filtered from the solution. The filtrate was collected, and the DMF removed *in vacuo*, yielding a dark yellow, oily residue. Methanol was added to the residue to remove excess aldehyde reagent and precipitate out the product. The resultant white suspension was stirred overnight, and the purified product was obtained by filtration from the methanol as a solid.

Tetraaldehyde 14. Application of the general procedure using tetrol **9** (0.50 g, 0.705 mmol) and aldehyde reagent **11** (1.45 g, 5.64 mmol) gave **14** (0.79 g, 71%) as an off-white solid (Found: C, 72.9; H, 7.2. $C_{96}H_{112}O_{20}$ requires C, 72.7; H, 7.2%); mp 60 °C dec. ν_{max}(KBr)/cm^{-1} 2921, 2851, 1682, 1597, 1436, 972; δ_H(400 MHz, $CDCl_3$) 0.93 (t, *J* 7.0 Hz, 12 H, C*H*$_3$), 1.39 (m, 24 H, (C*H*$_2$)$_3$), 1.80 (m, 8 H, O(CH$_2$)$_2$C*H*$_2$CH$_2$O), 2.03 (m, 8 H, O(CH$_2$)$_2$C*H*$_2$CH$_2$O), 2.16 (m, 8 H, CHC*H*$_2$(CH$_2$)$_3$CH$_3$), 3.99 (t, *J* 6.0 Hz, 8 H, O(CH$_2$)$_3$C*H*$_2$O) 4.16 (t, *J* 5.8 Hz, 8 H, O(CH$_2$)$_3$C*H*$_2$O), 4.41 (d, *J* 7.1 Hz, 4 H, inner of OC*H*$_2$O), 4.70 (t, *J* 7.6 Hz, 4 H C*H*(CH$_2$)$_4$CH$_3$), 5.79 (d, *J* 6.7 Hz, 4 H, outer of OC*H*$_2$O), 6.82 (s, 4 H, cavitand Ar *H*), 6.99 (m, 8 H, Ar *H*), 7.55 (t, *J* 7.4 Hz, 4 H, Ar *H*), 7.82 (d, *J* 7.4 Hz, 4 H, Ar *H*), 10.52 (s, 4 H, Ar C*H*O); δ_C(100 MHz, $CDCl_3$) 189.8, 161.5, 148.3, 144.4, 138.9, 136.0, 128.2, 124.9, 120.6, 114.2, 112.6, 99.5, 73.0, 68.2, 37.0, 32.1, 29.9, 27.6, 26.8, 25.9, 22.7,14.2.

Tetraaldehyde 15. Application of the general procedure using tetrol **9** (0.51 g, 0.705 mmol) and aldehyde reagent **12** (1.35 g, 5.55 mmol) gave **15** (0.92 g, 85%) as an off-white solid (Found: C, 72.3; H, 6.9. $C_{92}H_{104}O_{20}$ requires C, 72.2; H, 6.9%); mp 65 °C dec. ν_{max}(KBr)/cm^{-1} 2919, 2847, 1678, 1597, 1435, 971; δ_H(400 MHz, $CDCl_3$) 0.92 (t, *J* 7.1 Hz, 12 H, C*H*$_3$), 1.40 (m, 24 H, (C*H*$_2$)$_3$), 2.16 (m, 16 H, CHC*H*$_2$(CH$_2$)$_3$CH$_3$ and OCH$_2$C*H*$_2$CH$_2$O), 4.14 (t, *J* 5.8 Hz, 8 H, O(CH$_2$)$_2$C*H*$_2$O) 4.26 (t, *J* 6.1 Hz, 8 H, O(CH$_2$)$_2$C*H*$_2$O), 4.33 (d, *J* 7.0 Hz, 4 H, inner of OC*H*$_2$O), 4.64 (t, *J* 8.0 Hz, 4 H C*H*(CH$_2$)$_4$CH$_3$), 5.64 (d, *J* 7.1 Hz, 4 H, outer of OC*H*$_2$O), 6.80 (s, 4 H, cavitand Ar *H*), 7.00 (m, 8 H, Ar *H*), 7.51 (t, *J* 7.5 Hz, 4 H, Ar *H*), 7.83 (d, *J* 7.7 Hz, 4 H, Ar *H*), 10.49 (s, 4 H, Ar C*H*O); δ_C(100 MHz, $CDCl_3$) 189.7, 161.4, 148.1, 144.0, 139.0, 135.9, 128.3, 124.9, 120.6, 114.3, 112.5, 99.4, 76.7, 69.8, 65.2, 37.0, 32.1, 29.9, 29.7, 27.6, 22.7, 14.1.

Tetraaldehyde 16. Application of the general procedure using tetrol **9** (0.50 g, 0.705 mmol) and aldehyde reagent **13** (1.28 g, 5.59 mmol) gave **16** (0.93 g, 90%) as a white powder (Found: C, 71.9; H, 6.7. $C_{88}H_{96}O_{20}$ requires C, 71.7; H, 6.6%); mp 85 °C dec. ν_{max}(KBr)/cm^{-1} 2921, 2855, 1680, 1600, 1435, 970; δ_H(400 MHz, $CDCl_3$) 0.92 (t, *J* 6.9 Hz, 12 H, C*H*$_3$), 1.41 (m, 24 H, (C*H*$_2$)$_3$), 2.25 (m, 8 H, CHC*H*$_2$(CH$_2$)$_3$CH$_3$), 4.35 (m, 20 H, inner of OC*H*$_2$O and OC*H*$_2$C*H*$_2$O), 4.65 (t, *J* 7.4 Hz, 4 H C*H*(CH$_2$)$_4$CH$_3$), 5.75 (d, *J* 7.0 Hz, 4 H, outer of OC*H*$_2$O), 6.80 (s, 4 H, cavitand Ar *H*), 7.00 (m, 8 H, Ar *H*), 7.52 (t, *J* 7.5 Hz, 4 H, Ar *H*), 7.82 (d, *J* 7.3 Hz, 4 H, Ar *H*), 10.50 (s, 4 H, Ar C*H*O); δ_C(100 MHz, $CDCl_3$) 189.8, 161.3, 148.1, 144.0, 139.0, 135.9, 128.1, 125.1, 120.9, 114.5, 112.8, 99.3, 71.4, 68.2, 36.9, 31.9, 29.4, 27.6, 22.7, 14.2.

Tetraaldehyde 17. Application of the general procedure using tetrol **10** (0.51 g, 0.491 mmol) and aldehyde reagent **11** (1.00 g, 3.93 mmol) gave **17** (0.64 g, 76%) as an off-white powder (Found: C, 75.4; H, 6.1. $C_{108}H_{104}O_{20}$ requires C, 75.3; H, 6.1%); mp 102–104 °C dec. ν_{max}(KBr)/cm^{-1} 2940, 1681, 1595, 1383, 1288, 1244, 1183, 1157, 1104, 1020, 979, 837; δ_H(400 MHz, $CDCl_3$) 1.85 (m, 8 H, O(CH$_2$)$_2$C*H*$_2$CH$_2$O), 2.01 (m, 8 H, O(CH$_2$)$_2$C*H*$_2$CH$_2$O), 2.42–2.46 (m, 8 H, C*H*$_2$CH$_2$Ar), 2.61–2.65 (m, 8 H, CH$_2$C*H*$_2$Ar), 3.99 (t, *J* 6.1 Hz, 8 H, O(CH$_2$)$_3$C*H*$_2$O), 4.14 (t, *J* 5.9 Hz, 8 H, O(CH$_2$)$_3$C*H*$_2$O), 4.39 (d, *J* 7.0 Hz, 4 H, inner of OC*H*$_2$O), 4.79 (t, *J* 7.3 Hz, 4 H, C*H*CH$_2$CH$_2$Ar), 5.78 (d, *J* 7.2 Hz, 4 H, outer of OC*H*$_2$O), 6.82 (s, 4 H, cavitand Ar *H*), 6.99 (m, 4 H, Ar *H*), 7.12 (m, 4 H, Ar *H*), 7.18–7.22 (m, 20 H, CH$_2$CH$_2$C$_6$*H*$_5$), 7.51 (t, *J* 8.5 Hz, 4 H, Ar *H*), 7.80 (dd, *J* 7.8 Hz, *J* 1.8 Hz, 4 H, Ar *H*), 10.50 (s, 4 H, Ar C*H*O); δ_C(100 MHz, $CDCl_3$) 189.9, 161.5, 148.6, 144.6, 141.8, 138.7, 136.0, 128.6, 128.4, 128.3, 126.0, 120.6, 114.0, 112.5, 99.5, 73.8, 68.2, 62.7, 37.1, 34.5, 32.4, 29.7, 26.8, 25.9.

Tetraaldehyde 18. Application of the general procedure using tetrol **10** (0.50 g, 0.490 mmol) and aldehyde reagent **12** (0.95 g, 3.93 mmol) gave **18** (0.66 g, 81%) as an off-white powder (Found: C, 75.1; H, 5.9. $C_{104}H_{96}O_{20}$ requires C, 74.9; H, 5.9%); mp 96–100 °C dec. ν_{max}(KBr)/cm^{-1} 2944, 1684, 1598, 1387, 1285, 1240, 1188, 1152, 1103, 1047, 1018, 976, 841; δ_H(400 MHz, $CDCl_3$) 2.13–2.16 (t, *J* 6.0 Hz, 8 H, OCH$_2$C*H*$_2$CH$_2$O), 2.41–2.45 (m, 8 H, C*H*$_2$CH$_2$Ar), 2.60–2.64 (m, 8 H, CH$_2$C*H*$_2$Ar), 4.14 (t, *J* 5.8 Hz,

8 H, $O(CH_2)_2CH_2O$), 4.25 (t, *J* 6.0 Hz, 8 H, $O(CH_2)_2CH_2O$), 4.33 (d, *J* 7.1 Hz, 4 H, inner of OCH_2O), 4.74 (t, *J* 7.9 Hz, 4 H, $CHCH_2CH_2Ar$), 5.63 (d, *J* 7.1 Hz, 4 H, outer of OCH_2O), 6.79 (s, 4 H, cavitand Ar *H*), 6.98 (m, 4 H, Ar *H*), 7.13 (m, 4 H, Ar *H*), 7.18–7.24 (m, 20 H, $CH_2CH_2C_6H_5$), 7.50 (td, *J* 7.8 Hz, *J* 1.8 Hz, 4 H, Ar *H*), 7.81 (dd, *J* 7.9 Hz, *J* 1.9 Hz, 4 H, Ar *H*), 10.48 (s, 4 H, Ar CHO); δ_C(100 MHz, $CDCl_3$) 189.8, 161.4, 148.4, 144.4, 141.8, 138.9, 136.1, 128.7, 128.5, 126.1, 125.1, 120.8, 114.2, 112.6, 99.5, 70.0, 65.2, 37.2, 34.6, 32.52, 30.0.

Tetraaldehyde 19. Application of the general procedure using tetrol **10** (0.50 g, 0.490 mmol) and aldehyde reagent **13** (0.90 g, 3.93 mmol) gave **19** (0.74 g, 93%) as a white powder (Found: C, 74.7; H, 5.6. $C_{100}H_{88}O_{20}$ requires C, 74.6; H, 5.6%); mp 106–108 °C dec. ν_{max}(KBr)/cm^{-1} 2939, 2870, 1683, 1599, 1480, 1438, 1315, 1286, 1155, 1103, 1018, 980, 831; δ_H(400 MHz, $CDCl_3$) 2.39–2.46 (m, 8 H, CH_2CH_2Ar), 2.59–2.63 (m, 8 H, CH_2CH_2Ar), 4.33 (m, 20 H, inner of OCH_2O and OCH_2CH_2O), 4.72 (t, *J* 7.8 Hz, 4 H, $CHCH_2CH_2Ar$), 5.64 (d, *J* 7.1 Hz, 4 H, outer of OCH_2O), 6.80 (s, 4 H, cavitand Ar *H*), 6.99 (m, 4 H, Ar *H*), 7.16 (m, 4 H, Ar *H*), 7.18–7.24 (m, 20 H, $CH_2CH_2C_6H_5$), 7.52 (td, *J* 7.8 Hz, *J* 1.8 Hz, 4 H, Ar *H*), 7.80 (dd, *J* 7.9 Hz, *J* 1.7 Hz, 4 H, Ar *H*), 10.31 (s, 4 H, Ar CHO); δ_C(100 MHz, $CDCl_3$) 189.9, 161.3, 148.4, 144.3, 141.9, 138.9, 136.0, 128.2, 128.0, 126.1, 125.1, 121.0, 114.4, 112.9, 99.4, 71.5, 68.3, 37.1, 34.5, 32.3.

General procedure for preparation of capsules 20–25 using the Adler conditions with MW-assisted heating. Propionic acid (4 mL) was added to a borosilicate microwave reaction tube containing the appropriate tetraaldehyde. Once the material dissolved, freshly distilled pyrrole (four equivalents) was added, together with a small stirrer bar, and the tube sealed with a Teflon-lined cap. The tube was inserted into the microwave heating unit and heated rapidly whilst stirring to 160 °C. Once the temperature had been attained, it was maintained for five minutes, after which time the tube was allowed to cool to room temperature. The vessel was removed from the microwave, shielded from light and its cap removed, before being allowed to stir overnight in air. The reaction was carried out in quintriplicate. The collective vessel contents were subsequently poured into a separating funnel. Water (100 mL), saturated with $NaHCO_3$, and CH_2Cl_2 (100 mL) was added to the separating funnel, and the reaction mixture subsequently extracted *carefully*. The washing of the organic layer was repeated once more with aqueous $NaHCO_3$, and after effervescence subsided completely, the organic layer was dried over Na_2SO_4, filtered and preadsorbed onto silica (3 g). Initial silica gel chromatography using a mobile phase of 95:5 $CHCl_3$:EtOAc removed the majority of the polymeric material from the crude reaction product. Thereafter, a second column using a benzene eluant afforded a purified purple product. Once the benzene was removed *in vacuo*, the purple residue was dissolved in a small amount of $CHCl_3$, and methanol allowed to slowly diffuse into the solution in order to recrystallise the product. After 2–3 days, the capped porphyrin was isolated as a dark purple, microcrystalline solid.

Resorcin[4]arene cavitand-capped porphyrin 20. Application of the general procedure to tetraaldehyde **14** (0.100 g, 0.063 mmol) and pyrrole (0.017 g, 0.018 mL, 0.26 mmol) gave **20** (0.011 g, 10%) as a purple, microcrystalline solid (Found: C, 75.9; H, 6.8; N 3.2. $C_{112}H_{118}N_4O_{16}$ requires C, 75.7; H, 6.7; N 3.2%); mp >300 °C. ν_{max}(KBr)/cm^{-1} 3301, 2850,1438, 964; δ_H(400 MHz, $CDCl_3$) –2.81 (s, 2 H, NH), 0.81 (t, *J* 6.9 Hz, 12 H, CH_3), 1.28 (m, 32 H, $(CH_2)_3$ and $O(CH_2)_2CH_2CH_2O$), 1.46 (m, 8 H, $O(CH_2)_2CH_2CH_2O$), 1.95 (m, 8 H, $CHCH_2(CH_2)_3CH_3$), 3.20 (t, *J* 6.0 Hz, 8 H, $O(CH_2)_3CH_2O$), 3.45 (d, *J* 7.2 Hz, 4 H, inner of OCH_2O), 4.15 (t, *J* 6.4 Hz, 8 H, $O(CH_2)_3CH_2O$), 4.45 (t, *J* 8.0 Hz, 4 H $CH(CH_2)_4CH_3$), 5.40 (d, *J* 6.9 Hz, 4 H, outer of OCH_2O), 6.52 (s, 4 H, cavitand Ar *H*), 7.22 (t, *J* 8.4 Hz, 4 H, Ar *H*), 7.40 (d, *J* 8.4 Hz, 4 H, Ar *H*), 7.65 (d, *J* 7.4 Hz, 4 H, Ar *H*), 7.73 (t, *J* 8.6 Hz, 4 H, Ar *H*), 8.71 (s, 8 H, HC(β) of pyrrole); δ_C(100 MHz, $CDCl_3$) 158.1, 147.8, 144.0, 138.7, 136.6, 131.4, 129.6, 128.3,119.3, 115.9, 113.8, 111.9, 100.2, 73.2, 68.4, 36.6, 31.8, 30.9, 29.7, 29.6, 26.4, 26.1, 22.6, 14.1; *m/z* (ESI-TOF MS) calcd for $[M + H]^+$ 1776.8649, found 1776.7110; $\lambda_{max}(CH_2Cl_2)$/nm 417 (Soret, ε/dm^3 mol^{-1} cm^{-1} 44 950), 510 (1900), 544 (620).

Resorcin[4]arene cavitand-capped porphyrin 21. Application of the general procedure to tetraaldehyde **15** (0.100 g, 0.065 mmol) and pyrrole (0.017 g, 0.018 mL, 0.26 mmol) gave **21** (0.011 g, 10%) as a purple, microcrystalline solid (Found: C, 75.5; H, 6.6; N 3.3. $C_{108}H_{110}N_4O_{16}$ requires C, 75.4; H, 6.5; N 3.3%); mp >300 °C. ν_{max}(KBr)/cm^{-1} 3305, 2919, 2849,1438, 965; δ_H(400 MHz, $CDCl_3$) –2.81 (s, 2 H, NH), 0.87 (t, *J* 6.8 Hz, 12 H, CH_3), 1.25 (m, 24 H, $(CH_2)_3$), 1.46 (m, 8 H, $OCH_2CH_2CH_2O$), 1.88 (m, 8 H, $CHCH_2(CH_2)_3CH_3$), 3.25 (d, *J* 7.2 Hz, 4 H, inner of OCH_2O), 3.40 (t, *J* 5.6 Hz, 8 H, $O(CH_2)_2CH_2O$), 4.17 (t, *J* 5.8 Hz, 8 H, $O(CH_2)_2CH_2O$), 4.34 (t, *J* 8.1 Hz, 4 H $CH(CH_2)_4CH_3$), 5.20 (d, *J* 7.2 Hz, 4 H, outer of OCH_2O), 6.40 (s, 4 H, cavitand Ar *H*), 7.29–7.40 (m, 8 H, Ar *H*), 7.73 (t, *J* 8.7 Hz, 4 H, Ar *H*), 7.86 (d, *J* 7.4 Hz, 4 H, Ar *H*), 8.74 (s, 8 H, HC(β) of pyrrole); δ_C(100 MHz, $CDCl_3$) 158.4, 146.9, 143.5, 138.3, 136.8, 132.0, 130.0, 119.8, 115.8, 113.3, 113.1, 99.2, 69.2, 65.8, 36.5, 31.9, 31.8, 30.7, 27.4, 22.7, 22.5, 14.1; *m/z* (ESI-TOF MS) calcd for $[M + H]^+$ 1720.8023, found 1720.7948; $\lambda_{max}(CH_2Cl_2)$/nm 421 (Soret, ε/dm^3 mol^{-1} cm^{-1} 50 200), 511 (3600), 547 (1500).

Resorcin[4]arene cavitand-capped porphyrin 22. Application of the general procedure to tetraaldehyde **16** (0.100 g, 0.068 mmol) and pyrrole (0.018 g, 0.019 mL, 0.27 mmol) gave **22** (0.019 g, 17%) as a purple, microcrystalline solid (Found: C, 75.25; H, 6.4; N 3.4. $C_{104}H_{102}N_4O_{16}$ requires C, 75.0; H, 6.2; N 3.4%); mp >300 °C. ν_{max}(KBr)/cm^{-1} 3305, 2920, 2851,1435, 978; δ_H(400 MHz, $CDCl_3$) –2.90 (s, 2 H, NH), 0.80 (t, *J* 6.9 Hz, 12 H, CH_3), 1.19 (m, 24 H, $(CH_2)_3$), 1.85 (m, 8 H, $CHCH_2(CH_2)_3CH_3$), 3.10 (d, *J* 7.3 Hz, 4 H, inner of OCH_2O), 3.43 (t, *J* 5.7 Hz, 8 H, OCH_2CH_2O), 4.37 (m, 12 H, $CH(CH_2)_4CH_3$ and OCH_2CH_2O), 5.10 (d, *J* 7.3 Hz, 4 H, outer of OCH_2O), 6.30 (s, 4 H, cavitand Ar *H*), 7.35 (m, 8 H, Ar *H*), 7.76 (t, *J* 8.7 Hz, 4 H, Ar *H*), 7.87 (d, *J* 7.4 Hz, 4 H, Ar *H*), 8.74, 8.80 (both s, 8 H, HC(β) of pyrrole); δ_C(100 MHz, $CDCl_3$) 158.1, 146.6, 143.1, 138.2, 136.4, 131.4, 129.8, 119.9, 115.5, 113.2, 112.0, 99.3, 71.2, 67.8, 36.5, 31.8, 29.7, 27.3, 22.5, 14.0; *m/z* (ESI-TOF MS) calcd for $[M + H]^+$ 1664.7397, found 1664.7529; $\lambda_{max}(CH_2Cl_2)$/nm 418 (Soret, ε/dm^3 mol^{-1} cm^{-1} 47 100), 510 (2150), 543 (780).

Resorcin[4]arene cavitand-capped porphyrin 23. Application of the general procedure to tetraaldehyde **17** (0.075 g, 0.044 mmol) and pyrrole (0.012 g, 0.013 mL, 0.17 mmol) gave **23** (0.007 g, 8.0%) as a purple, microcrystalline solid (Found: C, 78.0; H, 6.1; N 3.0. $C_{124}H_{110}N_4O_{16}$ requires C, 77.8; H, 5.9; N 2.9%); mp >300 °C.

ν_{max}(KBr)/cm^{-1} 3308, 2926, 2850, 1595, 1472, 1258, 1150, 1110, 1044, 968, 799, 754; δ_H(400 MHz, $CDCl_3$) −2.81 (s, 2 H, N*H*), 1.30 (m, 8 H, O(CH_2)$_2$C*H*$_2$$CH_2$O), 1.49 (m, 8 H, O($CH_2$)$_2$C*H*$_2$$CH_2$O), 2.23–2.30 (m, 8 H, C*H*$_2$$CH_2$Ar), 2.44–2.48 (m, 8 H, CH_2C*H*$_2$Ar), 3.23 (t, *J* 5.9 Hz, 8 H, O(CH_2)$_3$C*H*$_2$O), 3.46 (d, *J* 7.1 Hz, 4 H, inner of OC*H*$_2$O), 4.15 (t, *J* 6.2 Hz, 8 H, O(CH_2)$_3$C*H*$_2$O), 4.43 (t, *J* 7.9 Hz, 4 H, C*H*$CH_2$$CH_2$Ar), 5.40 (d, *J* 7.2 Hz, 4 H, outer of OC*H*$_2$O), 6.54 (s, 4 H, cavitand Ar *H*), 6.97–6.99 (m, 8 H, $CH_2$$CH_2$$C_6$*H*$_5$), 7.10–7.12 (m, 12 H, $CH_2$$CH_2$$C_6$*H*$_5$), 7.29 (d, *J* 8.1 Hz, 4 H, Ar *H*), 7.42 (m, 4 H, Ar *H*), 7.63 (d, *J* 7.5 Hz, 4 H, Ar *H*), 7.72 (t, *J* 8.3 Hz, 4 H, Ar *H*), 8.70 (s, 8 H, *H*C(β) of pyrrole); 158.2, 147.3, 143.6, 141.6, 138.0, 136.8, 131.9, 130.7, 129.8, 128.7, 128.3, 128.2, 125.7, 120.0, 115.6, 113.1, 112.7, 99.2, 69.5, 65.7, 38.8, 36.6, 34.1, 32.0, 30.8, 26.7; *m*/*z* (ESI-TOF MS) calcd for [M + H]$^+$ 1912.8023, found 1912.7914; λ_{max}($CHCl_3$)/nm 417 (Soret, ε/dm^3 mol^{-1} cm^{-1} 45 900), 512 (2250), 544 (690).

Resorcin[4]arene cavitand-capped porphyrin 24. Application of the general procedure to tetraaldehyde **18** (0.075 g, 0.045 mmol) and pyrrole (0.012 g, 0.012 mL, 0.18 mmol) gave **24** (0.011 g, 13%) as a purple, microcrystalline solid (Found: C, 77.75; H, 5.7; N 3.1. $C_{120}H_{102}N_4O_{16}$ requires C, 77.6; H, 5.6; N 3.0%); mp >300 °C. ν_{max}(KBr)/cm^{-1} 3310, 2922, 2852, 1598, 1469, 1255, 1153, 1106, 1049, 966, 800, 750; δ_H(400 MHz, $CDCl_3$) −2.82 (s, 2 H, N*H*), 1.87 (m, 8 H, OCH_2C*H*$_2$$CH_2$O), 2.14–2.19 (m, 8 H, C*H*$_2$$CH_2$Ar), 2.40–2.43 (m, 8 H, CH_2C*H*$_2$Ar), 3.29 (d, *J* 7.4 Hz, 4 H, inner of OC*H*$_2$O), 3.44 (t, *J* 5.6 Hz, 8 H, O(CH_2)$_2$C*H*$_2$O), 4.19 (t, *J* 5.7 Hz, 8 H, O(CH_2)$_2$C*H*$_2$O), 4.44 (t, *J* 8.2 Hz, 4 H, C*H*$CH_2$$CH_2$Ar), 5.16 (d, *J* 7.4 Hz, 4 H, outer of OC*H*$_2$O), 6.39 (s, 4 H, cavitand Ar *H*), 6.95–6.97 (m, 8 H, $CH_2$$CH_2$$C_6$*H*$_5$), 7.09–7.10 (m, 12 H, $CH_2$$CH_2$$C_6$*H*$_5$), 7.30 (t, *J* 7.4 Hz, 4 H, Ar *H*), 7.38 (d, *J* 8.5 Hz, 4 H, Ar *H*), 7.72 (t, *J* 7.5 Hz, 4 H, Ar *H*), 7.85 (d, *J* 7.3 Hz, 4 H, Ar *H*), 8.73 (s, 8 H, *H*C(β) of pyrrole); δ_C(100 MHz, $CDCl_3$) 158.4, 147.1, 143.7, 141.6, 138.1, 136.8, 132.0, 130.8, 129.6, 128.8, 128.4, 128.2, 125.8, 119.8, 115.8, 113.2, 112.8, 99.1, 69.3, 68.1, 65.8, 38.7, 36.6, 34.2, 32.1, 30.7; *m*/*z* (ESI-TOF MS) calcd for [M + H]$^+$ 1856.7397, found 1856.5913; λ_{max}($CHCl_3$)/nm 420 (Soret, ε/dm^3 mol^{-1} cm^{-1} 43 800) 515 (2050), 549 (480).

Resorcin[4]arene cavitand-capped porphyrin 25. Application of the general procedure to tetraaldehyde **19** (0.075 g, 0.047 mmol) and pyrrole (0.013 g, 0.013 mL, 0.19 mmol) gave **25** (0.015 g, 18%) as a purple, microcrystalline solid (Found: C, 77.5; H, 5.35; N 3.1. $C_{116}H_{94}N_4O_{16}$ requires C, 77.4; H, 5.3; N 3.1%); mp >300 °C. ν_{max}(KBr)/cm^{-1} 3304, 2923, 1598, 1468, 1437, 1245, 1151, 1112, 1048, 1021, 978, 874; δ_H(400 MHz, $CDCl_3$) −2.88 (s, 2 H, N*H*), 2.12–2.18 (m, 8 H, C*H*$_2$$CH_2$Ar), 2.38–2.43 (m, 8 H, CH_2C*H*$_2$Ar), 3.14 (d, *J* 7.3 Hz, 4 H, inner of OC*H*$_2$O), 3.48 (t, *J* 5.6 Hz, 8 H, OCH_2C*H*$_2$O), 4.35 (t, *J* 5.5 Hz, 8 H, OC*H*$_2$$CH_2$O), 4.42 (t, *J* 7.9 Hz, 4 H, C*H*$CH_2$$CH_2$Ar), 5.12 (d, *J* 7.3 Hz, 4 H, outer of OC*H*$_2$O), 6.36 (s, 4 H, cavitand Ar *H*), 6.95–6.99 (m, 8 H, $CH_2$$CH_2$$C_6$*H*$_5$), 7.09–7.12 (m, 12 H, $CH_2$$CH_2$$C_6$*H*$_5$), 7.31–7.36 (m, 4 H, Ar *H*), 7.42 (d, *J* 8.4 Hz, 4 H, Ar *H*), 7.77 (td, *J* 7.3 Hz, *J* 1.8 Hz, 4 H, Ar *H*), 7.85 (dd, *J* 7.4 Hz, *J* 1.7 Hz, 4 H, Ar *H*), 8.71, 8.82 (both s, 8 H, *H*C(β) of pyrrole); δ_C(100 MHz, $CDCl_3$) 158.10, 158.03, 149.99, 146.76, 143.41, 141.58, 138.15, 138.07, 136.52, 131.49, 129.76, 128.44, 128.27, 125.89, 119.93, 115.49, 112.90, 112.13, 99.24, 71.29, 67.87, 36.58, 34.20, 32.22; *m*/*z* (ESI-TOF MS) calcd for [M + H]$^+$ 1800.6771, found 1800.5112; λ_{max}($CHCl_3$)/nm 419 (Soret, ε/dm^3 mol^{-1} cm^{-1} 46 800), 513 (2300) 546 (1150).

General procedure for the preparation of capped porphyrin capsules *via* the Adler reflux conditions. Stirring propionic acid (200 mL) in a 250 mL round-bottomed flask was heated to reflux in air. Once gently refluxing, tetraaldehyde was added to the reaction vessel and left to dissolve. On dissolution, the reaction vessel was shielded from light, and freshly distilled pyrrole (four equivalents) added to the solution. Over a period of approximately ten minutes, the reaction mixture went black. Reflux continued for a further 20 minutes, at which time the heating ceased, and the reaction was left to stir while slowly attaining room temperature. Work up and purification followed the procedure described for the reactions performed under microwave conditions.

Tetraaldehyde 27. To a stirring solution of tetrol **10** (0.50 g, 0.490 mmol) in dry THF (50 mL) under a nitrogen atmosphere, NaH (60% suspension in mineral oil, 0.16 g, 6.53 mmol) was added. To the resulting cream-coloured solution, **26** (0.68 g, 4.0 mmol) was added and the solution gently heated to reflux. The reaction continued for three days, during which time the solution assumed a grey colour. The reaction mixture was cooled to room temperature, and concentrated *in vacuo*. The products were chromatographed on silica gel using a mobile phase of 1:1 hexane–ethyl acetate. The eluant was concentrated under reduced pressure to give a yellow residue. Trituration of this residue with hexane yielded a white solid, which was collected and subsequently stirred in methanol to remove residual **26**. Filtration of this solution yielded **27** (0.26 g, 34%) as a white solid (Found: C, 74.5; H, 5.3. $C_{96}H_{80}O_{20}$ requires C, 74.2; H, 5.2%); mp 113–115 °C dec. ν_{max}(KBr)/cm^{-1} 2933, 1690, 1599, 1461, 1444, 1244, 1209, 1149, 1102, 1067, 977, 752; δ_H(400 MHz, $(CH_3)_2CO$) 2.43–2.49 (m, 8 H, C*H*$_2$$CH_2$Ar), 2.64–2.68 (m, 8 H, CH_2C*H*$_2$Ar), 4.44 (d, *J* 6.8 Hz, 4 H, inner of cavitand OC*H*$_2$O), 4.79 (t, *J* 7.9 Hz, 4 H, C*H*$CH_2$$CH_2$Ar), 5.39 (s, 4 H, OC*H*$_2$O), 5.96–5.99 (m, 8 H, outer of cavitand OC*H*$_2$O and extra-annular OC*H*$_2$O), 6.66 (s, 4 H, cavitand Ar *H*), 7.12–7.22 (m, 24 H, $CH_2$$CH_2$$C_6$*H*$_5$ and Ar *H*), 7.35 (d, *J* 8.4 Hz, 4 H, Ar *H*), 7.59 (t, *J* 7.8 Hz, 4 H, Ar *H*), 7.84 (d, *J* 7.7 Hz, 4 H, Ar *H*), 10.44 (s, 4 H, Ar C*H*O); δ_C(100 MHz, $(CH_3)_2CO$) 189.2, 143.5, 143.5, 143.3, 143.3, 143.2, 139.4, 136.9, 129.3, 129.2, 128.7, 126.6, 123.6, 116.4, 111.3, 100.7, 91.6, 38.1, 35.2, 33.0.

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41 The TPP derivative used consists as a mixture of four isomers, varying only in the orientation of the *o*-hydroxy groups. Isomerisation occurs at room temperature, and reflux of the reaction solution, as observed by Naruta and co-workers. This results in the correct orientation (over a period of days) of all the hydroxy groups to afford coupling of the porphyrin with the resorcin[4]arene. Altering reflux temperatures and lengths were among the changes made to protocol.
42 Preparation of supramolecularly capped porphyrins from aldehyde precursors such as **3** and **4** has been shown to proceed *via* two synthetic pathways. The most common of these two methods makes use of the Adler conditions; the addition of pyrrole to the aldehyde followed by condensation in an acidic medium (propionic acid) at reflux temperatures (140 °C) under aerobic conditions. In contrast, the gentler Lindsey conditions make use of a Lewis acid catalyst and dry, inert reaction conditions. This latter protocol has found only limited application. However, observations by Reinhoudt *et al.* indicated that porphyrin formation using this cyclisation technique was significantly dependant on the synthetic conditions employed. Ligands bearing shorter bridges formed exclusively on application of the Adler conditions, whilst ligands bearing longer bridges exclusively on application of the Lindsey conditions.
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