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Rings of Rings: Calixpyrrole Cyclotrimers

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Dedicated to Professor Philip Hodge for his outstanding contribution to the field of polymer chemistry

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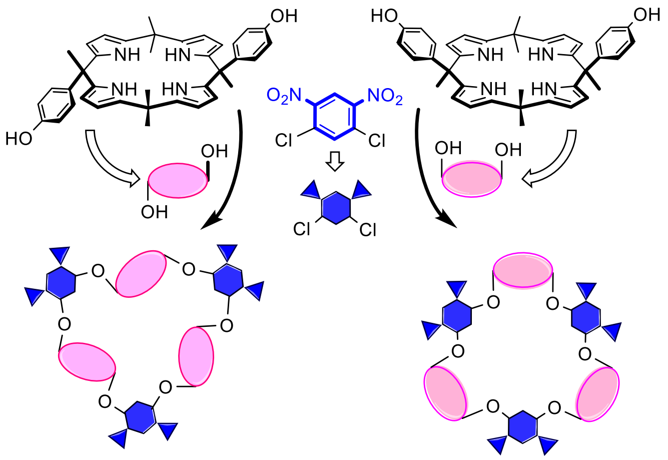
Abstract

Calixpyroles are a class of heteromacrocycles that have been a topic of considerable interest over the last two decades due to their rich host-guest chemistry as receptors for anions. A number of structures comprising more than one calixpyrrole unit have been reported as multitopic and multivalent receptors. Here we report the first syntheses of cyclotrimeric structures containing calixpyrrole rings (hence rings of rings) that can be obtained by the cyclo-oligomerization of either *cis*- or *trans*-1,3-*meso*-4-hydoxyphenyl-calix[4]pyrrole with 1,5-dichloro-2,4-dinitrobenzene via aromatic nucleophilic substitution reactions. The novel structures appear intriguing candidates for prospective molecular recognition studies.



Keywords: Calixpyrroles, macrocycles, cyclic oligomers, aromatic nucleophilic substitution.

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Introduction

Calixpyrroles are a class of macrocycles in which pyrrole units are connected by quaternary carbon atoms to form a macro-ring.[1] The discovery by J.L. Sessler that the earliest known *meso*-octamethyl-calix[4]pyrrole could act as a molecular receptor for anions[2] was followed by two decades of intense research leading to the development of a vast array of modified systems that can be used in a range of applications.[3-6] These include selective anion binding and transport across membranes,[7,8] the development of novel optical sensors,[9-10] several examples as organocatalysts,[11-13] and the discovery of potential antitumor properties for some specifically modified structures.[14] A number of expanded (more than 4 pyrrole units) and hybrid macrocycles in which aromatic units other than pyrroles are included as part of the macrocyclic structure have also been reported.[15-18] Functionalisation at the *meso* positions has been exploited for the tuning of the calixpyrrole properties,[19-24] and to include chemical moieties that can respond to external stimuli (e.g. stilbene or azobenzene units undergoing *cis*/*trans* isomerization by UV irradiation and thermally) providing a means to control the stability of complexes,[25] the formation of capsular assemblies,[26] or to modulate the binding selectivity of bis-calix pyrrole receptors towards bis-anions (bis-carboxylates) of different sizes.[27]

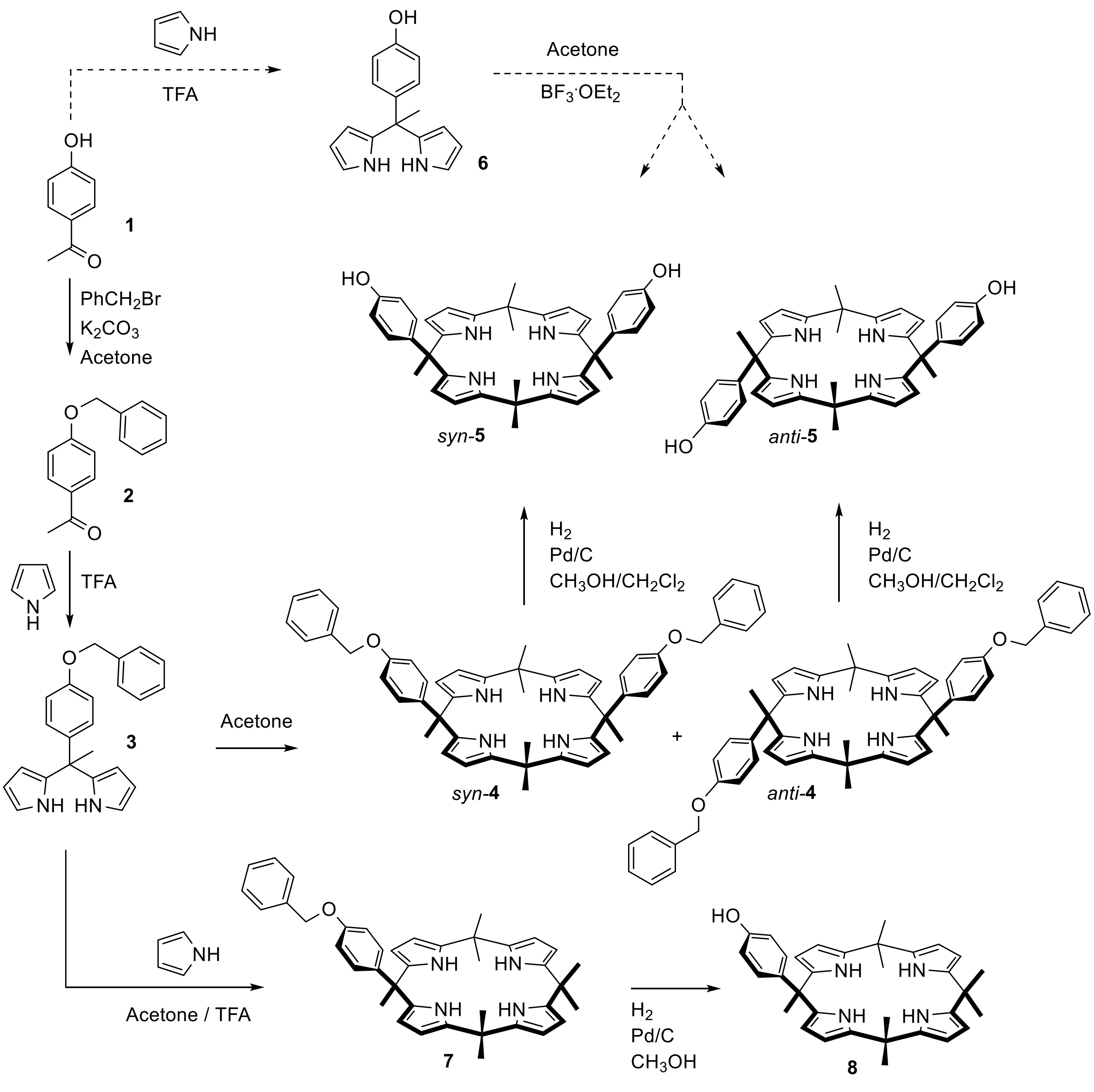
Multi calixpyrrole systems are of particular interest for their ability to either bind larger molecular guests at different (distant) sites of interactions (e.g. bis-anions like bis-carboxylates)[27] or for their potential ability to bring more than one guest species into close proximity, providing the basis for the development of novel materials that might act as synthetic enzymes.[5,28-30] However, few examples of multi (more than two) calixpyrrole systems have been described to date, especially if we exclude examples in which calixpyrrole units were grafted onto either polymers or surfaces. Notable examples of multicalixpyrrole structures (three or more calix units) have been reported by Ballester[31], Aoyan[32] and Kohnke.[33]

As part of our work on the host-guest chemistry of bis- and tris-calix[4]pyrrole[27,33] receptors, we identified the *anti*- and *syn*-*meso*-1,3-(4-hydroxyphenyl)calix[4]pyrroles (*anti*-**5** and *syn*-**5** in Scheme 1) first reported by Lee[34] as useful precursors for the assembly of multi-component structures. The potential to exploit the phenolate anions of *anti*-**5** and *syn*-**5** for the assembly of oligomeric structures via nucleophilic aromatic substitution reactions emerged from the past experience of one of us (FHK) as a visiting researcher in Professors P. Hodge and H. M. Colquhoun team in Manchester, and from being involved in the studies on ring-to-chain and chain-to-ring conversions of high performance polymers being conducted there at the time.[35,36] Moreover, phenol units grafted at the *meso*-position of calix[4]pyrroles were also used by Ballester in reactions with 1,2-difluoro-4,5-dinitrobenzene or 1,2-difluoro-4,5-dicyanobenzene to obtain calixpyrrole cavitands.[37] Inspired by these findings, we decided to explore the outcome of condensation reactions involving either *anti*-**5** or *syn*-**5** and 1,5-dichloro-2,4-dinitrobenzene **9** under basic conditions. In this paper we illustrate the outcome of this investigation.

Results and Discussion

The synthesis of calix[4]pyrroles having different substituents at distal *meso*-positions can be approached by a two-step procedure in which a pyrrole is initially reacted with a suitable ketone (4-hydroxyacetophenone for compounds **5**) to obtain the dipyrromethane **6**, which can then be reacted with acetone (Scheme 1, dotted arrows). This is indeed the method reported by Lee[34] to obtain compounds **5**. However, we found two major drawbacks with this method: i) the presence of the free phenolic unit contributes to the formation of tarry by-products during the synthesis of **6** and of compounds **5** and ii) the prevalent formation of *syn*-**5** (26%)

compared to *anti*-**5** (2%), this limiting the availability of the *anti*-stereoisomer for further synthetic studies. Therefore, we adopted the benzyl-ether protection strategy outlined in Scheme 1. Both the protection and deprotection steps proceeded with excellent yields, *syn*-and *anti*-**4** were formed in equal amounts (*ca* 20% each) and these were found to be quite resistant to degradation/decomposition during the operations required for their separation from the crude mixture as single isomers.

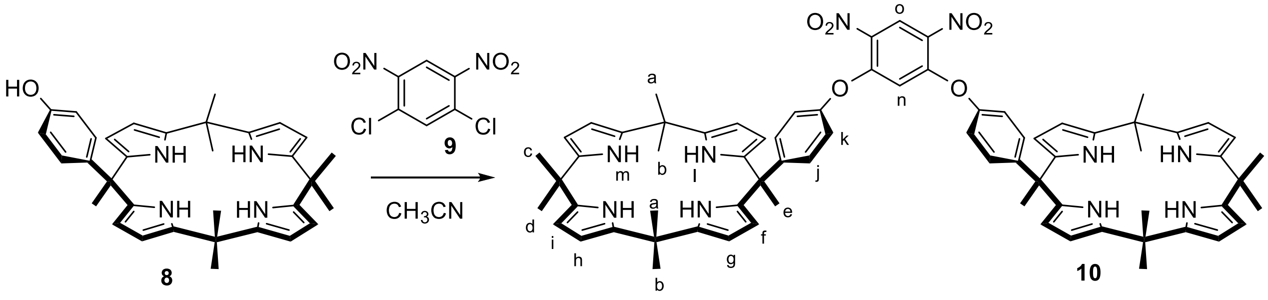


Scheme 1

Notably, compounds **4** can be described as 'super aryl extended calixpyrroles', never previously reported, and they are potentially intriguing molecular receptors. We noted that *syn*-**4** formed a molecular complex with adventitious formate ions present in the mass spectrometer much more efficiently than for *anti*-**4** or any of the other calixpyrrole derivatives reported here (see Figure S3d). The relative stereochemistries of compounds

4 were easily assigned from their ^{1}H NMR spectra, as the resonances are consistent with a time-averaged planar conformation of the macrocycle; the geminal methyl groups are equivalent in the *anti*-isomer and different in the C_{2v} symmetric *syn*-isomer. All other NMR signals were consistent with the indicated structure. Since the catalytic hydrogenation for the deprotection of the phenol units was conducted on isomerically pure *anti*-**4** or *syn*-**4** there was no ambiguity for the stereochemistry of compounds **5**, which can nevertheless be confirmed by their ^{1}H and ^{13}C NMR spectra on the basis of the same considerations made for compounds **4** (see Figures S2a, S2b, S3a, S3b for compounds **4,** and S4a, S4b, S5a, S5b for compounds **5**).

Before exploring the reactions of compounds **5** with 1,5-dichloro-2,4-dinitrobenzene **9**, we decided to prepare the bis-calixpyrrole **10** (Scheme 2) using *meso*-(4-hydroxypheny)calixyrrole **8**. This compound was expected to provide a tool to aid the identification of the NMR signals in the more complex mixtures that can arise from the reaction of compounds **5** with **9**. This required the synthesis of *meso*-(4-hydroxypheny)calixyrrole **8**, for which we decided to use dipyrromethane **3** as starting material via the intermediate **7**, since protection/deprotection strategy of the phenolic unit had proven to be advantageous. Compound **8** exhibits very different ^{1}H NMR spectra in $CDCl_3$ and DMSO-d_6 (compare Figures. S7a vs S7e). In DMSO the NH resonances are shifted downfield (from δ 7.23 and 7.30 to 9.37 and 9.51 respectively) indicating a strong hydrogen-bonding interaction with the solvent, the AB system associated with the pyrrole β-CH is considerably narrower, the AA'BB' system of the aryl unit is also very narrow, and the resonances of the geminal methyl groups that are closely packed in $CDCl_3$ appear much more spaced out in DMSO.



Scheme 2. The letters correlate to ^{1}H NMR assignments shown in Figure 1.

A variety of polar solvents and bases have been used for the nucleophilic substitution reaction of halogenated nitrobenzenes with phenols.[37] In this initial investigation we selected acetonitrile and either K_2CO_3 or CS_2CO_3.

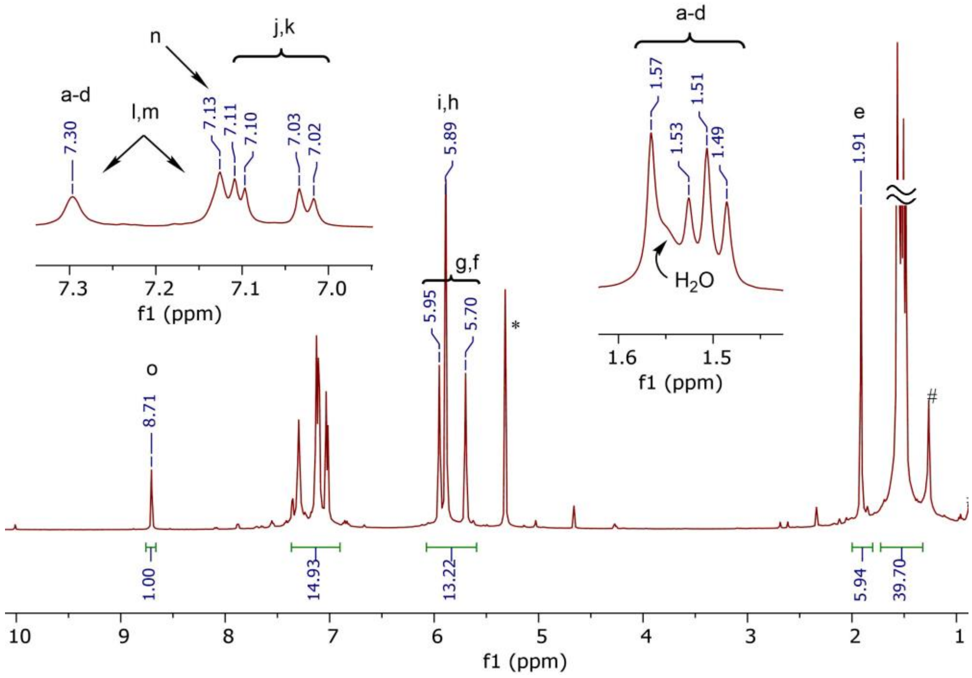
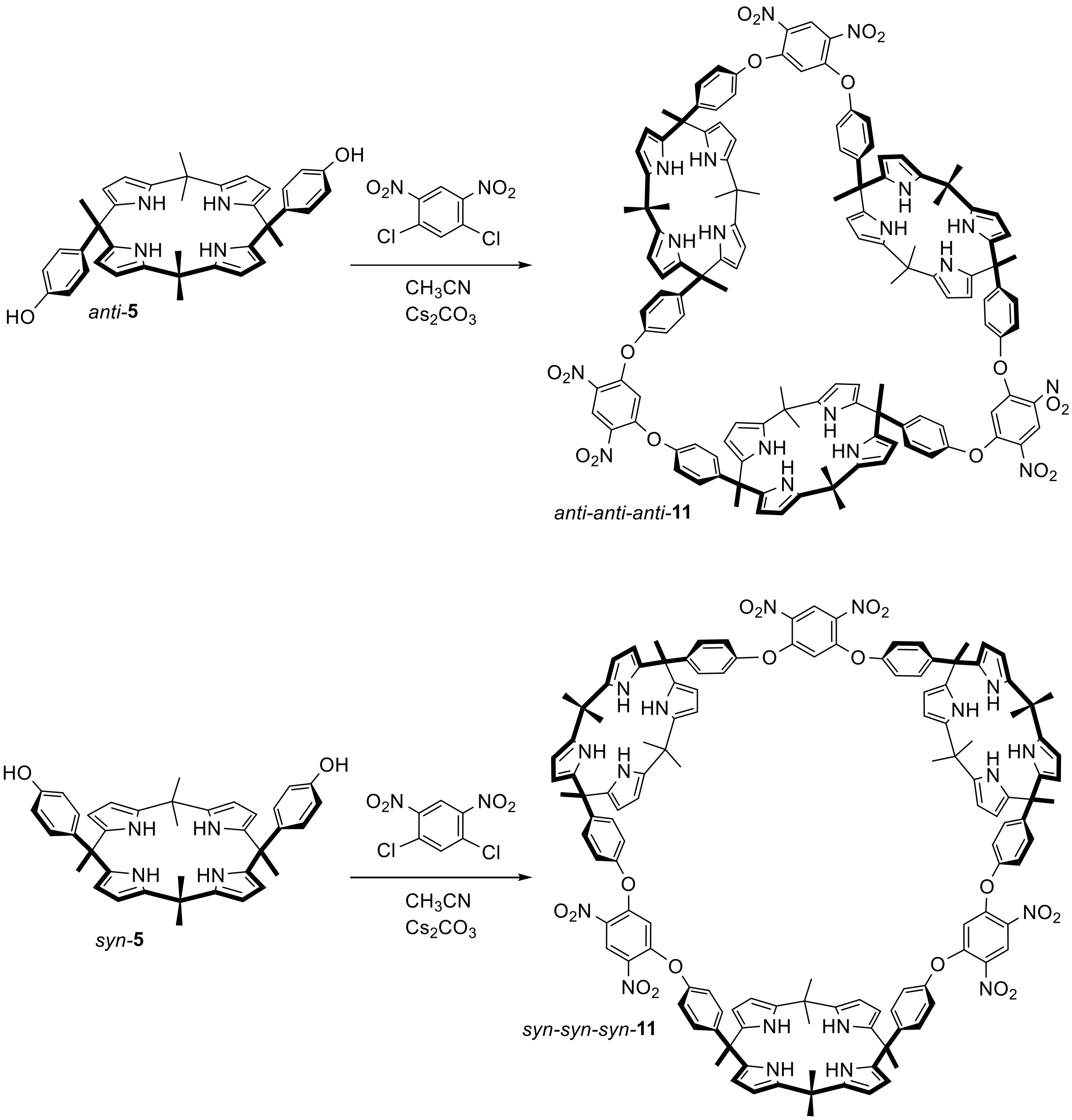


Figure 1. Partial ^{1}H NMR (500 MHz, DMSO-*d*$_6$) of **10**. Letters correlate to Scheme 2. * DCM, # solvent impurity.

The reaction of **9** with two molar equivalents of **8** gave bis-calixpyrrole **10** as the main product, albeit in moderate yield (25%). The ^{1}H NMR spectrum in CD_2Cl_2 (Figure 1, see Figure S8a for the ^{1}H NMR spectrum in DMSO-*d*$_6$) shows the presence of a singlet for the aryl proton placed between the nitrogroups at 8.71 ppm, but the resonance for the other proton on this ring is overlapping part of the AA'BB' system for the *p*-substituted aryl rings and one of the two signals for the two different sets of pyrrole NH units. This can be seen in the HSQC spectrum (Figure S8e) by the presence of a correlation with the carbon atom at 121.6 ppm. Five resonances are visible for the different sets of methyl groups (a broad signal between 1.57 and 1.53 ppm is ascribed to residual water) and the spectrum is consistent with a dynamically mediated conformation having a σ-plane perpendicular to the central aryl unit and passing across its CH groups. The new bis-calixpyrrole **10** has the potential to behave as a ditopic receptor for anions. Moreover, the nitrogroups can be subjected to a number of chemical transformations (e.g. reduction and derivatization) for the construction of complex and fascinating multi- or polycalixpyrrole systems.



Scheme 3

The condensation of **9** with the bis-phenolic calixpyrroles (Scheme 3) was initially tested using *syn*-**5**. Intuitively, but wrongly, we assumed that *anti*-**5** could not provide the 'concave' shape needed for macrocyclization. The selected reaction conditions were similar to those used for **10**, but we adopted Cs_2CO_3 as the base. This base was chosen to benefit from its higher solubility in CH_3CN compared to K_2CO_3 but we also hoped that the Cs^+ ions could favor the macrocyclization process by reducing the conformational flexibility of the calix[4]pyrrole units. In fact, calix[4]pyrroles may act as ditopic receptors, and host small cationic species (Cs^+ better suited than K^+) in the π-electron rich cavity that is formed by the pyrrole rings when the calix adopts a cone conformation (NH units pointing to an anionic counterion). The CsCl formed *in situ* was expected to reduce the conformation mobility of the calixpyrrole units, hence rendering the cyclization reactions less entropically unfavorable. While these considerations on the selection of the base Cs_2CO_3 have still to be assessed quantitively (e.g. evaluating the yield with different bases) the use of Cs_2CO_3 as base appeared to give cleaner reactions (lower number of spots on t.l.c.) than K_2CO_3. We were surprised to find that the reaction of **9** with either *anti*- or *syn*-**5** provided in both cases a crude mixture from which the only macrocyclization products that we were able to isolate by column chromatography were the cyclotrimers *anti-anti-anti*-**11** and *syn-syn-syn*-**11** respectively, although analysis of the other chromatographic fractions (^{1}H NMR) revealed the presence of linear oligomers. Yields of cyclotrimers **11** were very modest and were not optimized, but they might be increased by the use of high dilution techniques. The cyclic nature of these compounds is evident from their ^{1}H NMR spectra (Figures S9a-d and S10a-c). In fact, the calixpyrrole components maintain their symmetric properties (and hence their original pattern of proton resonances) only if included in a macroring (or equally derivatized at each phenolic oxygen). The trimeric structures were confirmed by mass spectrometry. These macrocycles were sparingly soluble in all organic solvents, and the acquisition of ^{13}C NMR spectra in which all carbon atoms are visible was severely compromised. However, close inspection of the observable carbon resonances in comparison with those of the related precursors allowed the assignment of most signals (see experimental section).

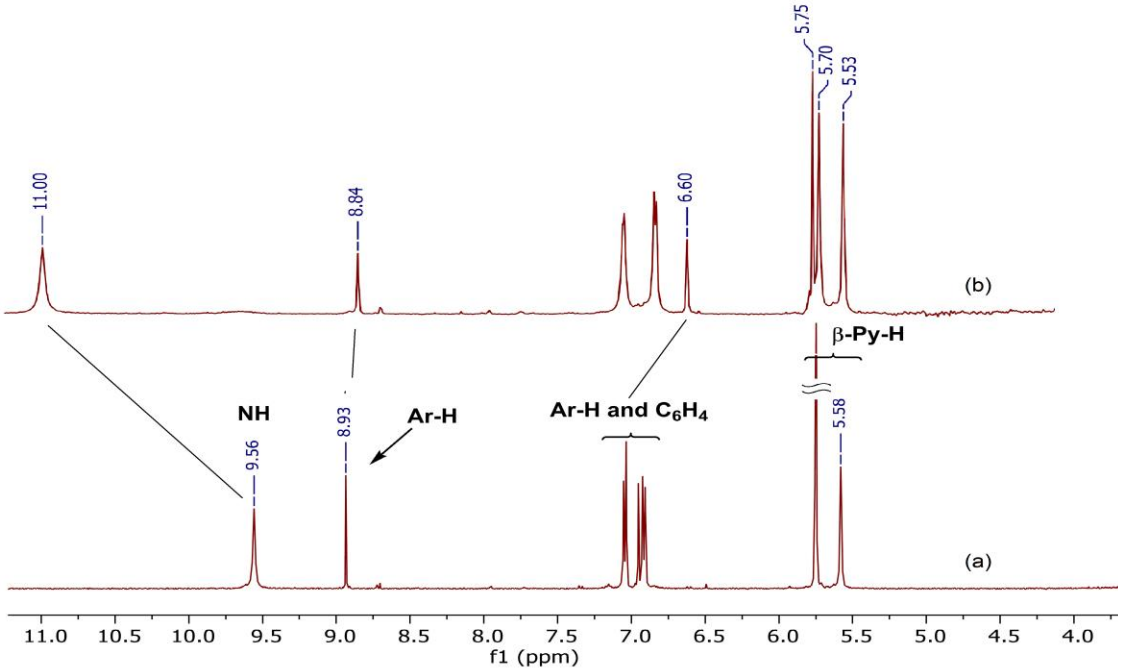


Figure 2. Partial ^{1}H NMR (500 MHz, DMSO-d_6) of *syn-syn-syn*-**11** in the absence (a) and in the presence (b) of an excess of TBACl.

The ^{1}H NMR of *syn-syn syn*-**11** in DMSO-d_6 shows all the resonances (see assignments in Figure S10a) that can be expected, including three well-resolved signals for the three sets of ‘different’ CH_3 units. The NH resonances at low field indicate a strong hydrogen-bonding interaction with the DMSO solvent. Although we have not had the opportunity to undertake host-guest binding studies, we explored the effects of TBACl on the ^{1}H NMR spectrum of *syn-syn syn*-**11** (Figure 2(b) and S10b). The presence of chloride produced remarkable complexation-induced shifts, most notably the NH resonances are shifted from 9.56 to 11.00 ppm, the aryl CH between the nitro groups is marginally affected (from 8.93 to 8.84 ppm) but the other aryl proton on the same aryl ring is shifted upfield (from 6.95 to 6.60 ppm). The overall number of resonances (general pattern) is unchanged in this chloride complex formed in the presence of a large excess of chloride. Therefore, the supramolecular chloride complex of *syn-syn-syn*-**11** and the free receptor appear to retain a D_{3h} symmetry which may result from either a dynamically mediated spectrum on the NMR time-scale or from a frozen conformation (the latter appears less likely). We speculate that three chloride ions are bound by *syn-syn-syn* **11** because the 'downfield effect' on the NH resonances for this interaction is consistent with that observed for typical 1:1 complexes of calix[4]pyrroles involving four NH units and one chloride. If only one chloride was involved in the formation of the complex with *syn-syn-syn*-**11**, one would expect the downfield effect to be smaller, being 'diluted' over three calix units (i.e. one or two chlorides spreading their effects over 12 NH units).

Conclusions

In this work we have demonstrated that calix[4]pyrrole derivatives containing nucleophilic phenol units at their distal *meso*-positions may be subjected to polymerization with 1,3-dichloro-4,5-dinitrobenzene to give both polymeric materials (not isolated and characterized in this study) and cyclooligomers. In this work only [3+3] cyclization products could be fully characterized. Surprisingly, both *syn*- and *anti*-**5** gave cyclotrimers, as one would expect that *anti*-**5,** which lacks the 'convergent' nature of the reactive groups, should not form small macrocyclization products, and certainly not ones of the same size as *syn*-**5**. Preliminary molecular modeling studies indicate that cyclotrimers **11** are essentially strain-free, all bonds and angles being within the expected ranges. The synthesis of these novel 'rings of rings' here obtained in modest yields may be improved, now that we have found that they can be made. This would provide the means to explore their host-guest chemistry in detail. Their large cavities can host multiple anions and biologically important ones. We have previously explored the biological activity of calixpyrrole derivatives on cancer cells, and these new compounds are intriguing candidates. Finally, the presence of nitroaromatic units provides a means for the chemical elaboration of these structures and a route to resolve the encountered solubility issues.

Experimental Section

General.

Starting reagents were purchased from commercial sources (Sigma-Aldrich and VWR International) and used as supplied. Solvents were dried/purified by conventional methods; pyrrole was distilled at reduced pressure shortly before use. Air/moisture sensitive reactions were conducted under Argon atmosphere. The progress of reactions was monitored by thin layer chromatography (t.l.c.) using Merck SiO_2 60F254 plastic plates; compounds were visualized with I_2 vapors and/or by examination under UV light.

Column chromatography was conducted using silica gel (Aldrich, 230-400 mesh, 60 Å). Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 500 spectrometer at 500 and 125 MHz, respectively, with the residual proton resonances of the solvents ($CDCl_3$, CD_2Cl_2, and DMSO-d_6) used as references. Chemical shifts are given in δ values on the ppm scale. The abbreviation Cq indicates quaternary carbon atom(s). For mass spectra measurements each sample (powder) was dissolved in acetonitrile (final concentration 1 mM) and analyzed by flow injection mass spectrometry (FIA-MS). Sample solutions (2 µl/min) were injected by means of an automated syringe into an eluent flow of acetonitrile generated by a Vanquish UHPLC system (Thermo Fisher Scientific). The flow rate was 100 µl/min. The eluent was directly sent to a Q-Exactive Plus Orbitrap mass spectrometer

(ThermoScientific - San Jose, USA) equipped with a heated electrospray ion source (HESI-II). Prior to each series of acquisitions, the mass spectrometer was externally calibrated with the Negative Ion Calibration Solution (Thermo Fisher Scientific). The following operating parameters were applied: resolution 140,000; sheath and auxiliary gas flow rate 35 and 10 respectively; spray voltage 3.0 kV; capillary temperature 250 °C; S-lens RF level 100. The autogain control (AGC) was optimized at 1e6 with a maximum injection time (maxIT) of 250 ms. Full scan data were processed with Xcalibur version 4.1 (ThermoScientific - San Jose, USA). High resolution mass spectra were acquired in negative ion mode and the identity of each analyte was confirmed by comparing the experimental data with both their theoretical molecular weight and their expected isotopic pattern. In the following experimental details calculated masses are given for the monoisotopic composition, found masses are for the statistically most significant isotopic composition.

4'-Hydroxyacetophenone **1** was acquired from Merck (Sigma-Aldrich); 4-Benzyloxyacetophenone **2** was prepared as reported previously.[39]

5-Methyl-5-(4-benzyloxyphenyl)dipyrromethane (3). 4-Benzyloxyacetophenone **2** (2.5 g, 11.0 mmol) was added to pyrrole (5.16 g, 5.3 mL, 77.0 mmol). The mixture was cooled to 0 °C and stirred under Ar atmosphere before adding trifluoroacetic acid (1.25 g, 0.84 mL, 11 mmol). Stirring was maintained for 24 h while the mixture was allowed to reach room temperature. A white/grey precipitate was formed. The acid was neutralized by the addition of aqueous saturated solution of $KHCO_3$ and the pasty mixture transferred onto a sintered filtering funnel with the aid of additional water. After removal of excess pyrrole and water the mixture was suspended in cold ethanol (10 ml) and filtered. The white solid (2.4 g, 63%) appeared pure (t.l.c. SiO_2, $PhCH_3$/EtOAc 8:2 showed a single spot with R_f *ca* 0.3). A small sample was recrystallised from EtOH: m.p. 116-114 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.17 (s, 3H, CH_3), 5.04 (s, 2H, CH_2), 5.96 and 6.17 (2 x m, 2H, pyrrole β-CH), 6.66 (m, 2H, pyrrole α-CH), 6.88 and 7.02 (2 x d, 2 x 2H, AA'BB', Ar-H), 7.33, 7.39, 7.42 (3 x m, 1H, 2H, 2H, Ar-H), 7.79 (brs, 2H, NH); ^{13}C NMR ($CDCl_3$) δ: 28.9 (CH_3), 44.3 (Cq), 70.0 (CH_2), 106.1, 108.2, 114.3 (CH-Py), 116.7, 127.4, 127.9, 128.5, 128.6 (Ar-CH), 137.3, 138.0, 140.0, 157.7 (Cq). Calculated *m/z* for $C_{23}H_{20}N_2O_2$ 342.1732; found ESI-MS $[M-1]^-$: 341.1656.

10α,20β-di(4-benzyloxyphenyl)calix[4]pyrrole (*anti*-4) and 10α,20α-di(4-benzyloxyphenyl)calix[4]pyrrole (*syn*-4). TFA (1.12 mL, 14.56 mmol) was added to a solution of **3** (2.5 g, 7.31 mmol) in dry acetone (100 mL), at 0 °C. The mixture was stirred under argon atmosphere at room temperature for 24 h, then neutralised by the addition of aqueous saturated solution of $NaHCO_3$ and diluted with DCM (50 mL). The mixture was transferred into a separating funnel, the aqueous phase was removed, and the organic solution was washed with H_2O (2 x 50 mL), then dried ($MgSO_4$), filtered and concentrated to yield a brown oil that was subjected to column chromatography (SiO_2, Hexane/EtOAc, 9:1) to give, in order of elution *anti*-**4** and *syn*-**4** (R_f values 0.7 and 0.6, respectively). *anti*-**4** (600 mg, white solid, 21%, m.p. 183 °C from acetone); ^{1}H NMR (CD2Cl$_2$) δ: 1.52 (s, 12H, CH_3), 1.86 (s, 6H, CH_3), 5.04 (s, 4H, CH_2), 5.74 and 5.90 (2 x m, 2 x 4H, pyrrole β-CH), 6.86 and 7.10 (AA'BB' system, 2 x 4H, Ar-CH), 7.19 (brs, 4H, pyrrole-NH), 7.33-7.44 (m, 10H, Ar-CH); ^{13}C NMR (CD_2Cl_2) δ: 29.5, 31.2 (CH_3), 35.75, 44.3 (Cq), 70.3 (CH_2), 103.4, 105.8, (CH-Py), 114.3, 127.8, 128.2, 128.7, 128.8 (Ar-CH), 136.9, 137.3, 139.1, 140.1, 157.8 (Cq). Calculated *m/z* for $C_{52}H_{52}N_4O_2$ 764.4090; found ESI-MS $[M-1]^-$: 763.4016. *syn*-**4** (560 mg 20%, white solid, m.p. 255 °C from acetone): ^{1}H NMR (CD_2Cl_2) δ: 1.53, 1.61, 1.87 (3 x s, 3 x 6H, CH_3), 5.02 (s, 4H, CH_2), 5.61 and 5.91 (2 x m, 2 x 4H, pyrrole β-CH), 6.84 and 6.87 (AA'BB' system, 2 x 4H, Ar-CH), 7.22 (br, s, 4H, pyrrole-NH), 7.42 (m, 10H, Ar-CH); ^{13}C NMR (CD_2Cl_2) δ: δ 27.5, 28.1, 30.6 (CH_3), 35.5, 44.5 (Cq), 70.5 (CH_2), 103.6, 106.3, (CH-Py), 114.3, 128.1, 128.4, 128.9, 129.1 (Ar-CH), 137.4, 137.9, 139.1, 141.1, 157.8 (Cq). Calculated *m/z* for $C_{52}H_{52}N_4O_2$ 764.4090; found ESI-MS $[M-1]^-$: 763.4016.

10α,20β-di(4-hydroxylphenyl)calix[4]pyrrole (*anti*-5) and 10α,20α-di(4-hydroxylphenyl)calix[4]pyrrole (*syn*-5). Palladium on carbon (10% w/w, 20% w/w catalyst/compound) was added to a solution of *anti*-**4** or *syn*-**4** (200 mg, 0.262 mmol) in a mixture of methanol/CH_2Cl_2 2:1, 60 mL. The suspension was stirred under hydrogen atmosphere at room temperature for 3 h. The reaction mixture was filtered through a pad of celite and concentrated under reduced pressure. The white solids were characterized without further purification (135 mg, 88%). *anti*-**5:** m.p. 200 °C dec., litt.[40] 360 °C; ^1H NMR (500 MHz, $CDCl_3$:CD_3OD) δ: 1.39 (s, 12H, CH_3), 1.70 (s, 6H, CH_3), 5.79 (m, 8H, pyrrole β-CH), 6.55 and 6.71 (AA'BB' system, 2 x 4H, Ar-CH), 8.44 (brs, 4H, pyrrole-NH); ^{13}C NMR (125 MHz, $CDCl_3$:CD_3OD) δ: 30.0, 30.1 (CH_3), 35.4, 43.9 (Cq), 102.5, 104.4, (CH-Py), 114.4, 128.3 (Ar-CH), 137.2, 138.9, 139.3, 154.7 (Cq). Calculated *m/z* for $C_{38}H_{40}N_4O_2$ 584.3151; found ESI-MS $[M-1]^-$: 583.3087. *syn*-**5**: m.p. 212 °C dec.; ^1H NMR (500 MHz, $CDCl_3$/CD_3OD 6:1) δ: 1.40, 1.51, 1.72 (3 x s, 3 x 6H, CH_3), 5.57 and 5.78 (2 x m, 2 x 4H, pyrrole β-CH), 6.56 and 6.67 (AA'BB' system, 2 x 4H, Ar-CH), 7.98 (brs, 4H, pyrrole-NH); ^{13}C NMR (125 MHz, $CDCl_3$/CD_3OD 6:1) δ: 28.1, 28.5, 29.4 (CH3), 34.9, 43.8 (Cq), 102.2, 105.1, (CH-Py), 114.2, 128.3 (Ar-CH), 137.5, 139.0, 139.4, 154.7 (Cq). Calculated *m/z* for $C_{38}H_{40}N_4O_2$ 584.3151; found ESI-MS $[M-1]^-$: 583.3084.

***meso*-(4-benzyloxyphenyl)-*meso*-heptamethyl-calix[4]pyrrole (7).** TFA (0.45 mL, 5.8 mmol) was added to a solution of **2** (2 g, 5.84 mmol), pyrrole (2 mL, 29.2 mmol), and acetone (4.29 mL, 58.5 mmol) in dry CH_2Cl_2 (100 mL), at 0 °C. The mixture was stirred under Ar atmosphere at room temperature for 24 h, then neutralized (NaOH 1M) and extracted with H_2O (2 x 50 mL). The organic phase was dried ($MgSO_4$) and concentrated. The brown solid residue was crystallized from $PhCH_3$:CH_2Cl_2 (9:1) to remove a large amount of octamethyl calix[4]pyrrole that is also formed and can be separated by filtration. The organic solution was subjected to column chromatography (SiO_2, $PhCH_3$:CH_2Cl_2, 9:1) to give **7**: (800 mg, 23%, m.p. 181-182°C from acetone). ^1H NMR (500 MHz, CD_2Cl_2) δ: 1.47, 1.50, 1.52, 155 (4 x s, 3H, 6H, 3H, 6H, CH_3), 1.85 (s, 3H, CH_3), 5.03 (s, 2H, CH_2), 5.66 (m, 2H, pyrrole β-CH), 5.85 (m, 4H, pyrrole β-CH), 5.90 (m, 2H, pyrrole β-CH), 6.84 and 6.92 (AA'BB' system, 2 x 4H, Ar-CH), 7.09 and 7.20 (2 x brs, 4H, pyrrole-NH), 7.39-7.46 (m, 5H, Ar-CH); ^{13}C NMR (125 MHz, CD_2Cl_2) δ: 27.5, 27.7, 28.3, 29.9, 30.0 (CH_3), 35.3, 35.3, 44.3 (Cq), 70.2 (CH_2), 103.0, 103.1, 103.3, 106.0 (pyrrole β-CH), 114.1, 127.8, 128.2, 128.7, 128.8 (Ar-CH), 137.0, 137.6, 138.5, 138.7, 139.0, 140.6, 157.6 (Cq). Calculated *m/z* for $C_{40}H_{44}N_4O$: 596.3515; found ESI-MS $[M-1]^-$:595.3445.

***meso*-(4-hydroxyphenyl)-*meso*-heptamethyl-calix[4]pyrrole (8).** Palladium on carbon (10% w/w, 20% w/w catalyst/compound) was added to a solution of **7** (200 mg, 0.335 mmol) in methanol (40 mL). The reaction mixture was stirred under hydrogen at room temperature for 2 h, then the suspension was filtered through a pad of celite, and concentrated under reduced pressure. The white solid was characterized without further purification (140 mg, 83%, m.p. 199 °C from methanol); ^1H NMR (500 MHz, $CDCl_3$) δ: 1.51, 1.52, 1.55 (3 x s, 3 x 6H, CH_3), 1.84 (s, 3H, CH_3), 5.27 (brs, 1H, PhOH), 5.66 (m, 2H, pyrrole β-CH), 5.90 (m, 6H, pyrrole β-CH), 6.68 and 6.97 (AA'BB' system, 2 x 2H, Ar-CH), 7.23 and 7.30 (2 x s, 2 x 2H, pyrrole-NH); ^1H NMR (500 MHz, DMSO-d_6) δ: 1.40, 1.46, 1.50, 1.56, 1.67 (5 x s, 3H, 6H, 3H, 6H, 3H, CH_3), 5.68-574 (m, 8H, pyrrole β-CH), 6.60-6.65 (AA'BB' system, 2x2H, Ar-CH), 9.23 (brs, 1H, PhOH) 9.37 and 9.51 (2 x brs, 2 x 2H, pyrrole-NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.4, 28.8, 28.9, 29.9, 30.2 (CH_3), 35.4, 35.5, 44,2 (Cq), 102.9, 103.2, 105.8 (pyrrole β-CH), 114.64, 128.8 (Ar-CH), 137.2, 138.6, 138.8, 138.9, 140.1, 154.3 (Cq). Calculated *m/z* for $C_{33}H_{38}N_4O$: 506.3046; found ESI-MS $[M-1]^-$:595.3445.

Bis-calixpyrrole 10.

Calixpyrrole **8** (200 mg, 0.4 mmol) and K_2CO_2 (70 mg, 0.47 mmol) were suspended in CH_3CN (50 ml) and refluxed under an Ar atmosphere for a few minutes, then cooled to room temperature before adding **9** (55 mg, 0.23 mmol) previously dissolved in CH_3CN (2 ml). The mixture was then refluxed for 2h and stirred at room temperature for 12h, then filtered to remove the solid residue. The organic phase was concentrated, redissolved in DCM, extracted with water, dried ($MgSO_4$), concentrated, and subjected to column chromatography (SiO_2, $PhCH_3$/DCM, 100% $PhCH_3$ to 100% DCM gradient) to give a reddish solid that was characterised as bis-calixpyrrole **10** (50 mg, 25%, 230 °C dec.) ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.43, 1.47, 1.52, 1.58, 1.79 (5 x s, 3H, 6H, 3H, 6H, 3H, CH_3), 5.72 and 5.75 (2 x m, 2 x 8H, pyrrole β-CH), 6.93 and 6.94 (AA'BB' system, 2 x 2H, Ar-CH), 7.15-7.30 (AA'BB' system, 2 x 2H with overlapping residual $PhCH_3$, Ar-CH, 2 x 2H, Ar-CH), 7.41 (s, 1H, Ar-H), 8.94 (s, 1H, Ar-H), 9.31 and 9.57 (2 x brs, 2 x 4H, 2 x NH); ^{1}H NMR (500 MHz, CD_2Cl_2) δ: 1.49, 1.51, 1.52, 1.57, 1.91 (5 x s, 3H, 6H, 3H, 6H, 3H, CH_3), 5.70 and 5.95 (2 x m, 2 x 4H, pyrrole β-CH), 5.89 (m, 2 x 4H, pyrrole β-CH), 7.02 and 7.10 (AA'BB' system, 2 x 4H, Ar-CH), 7.13 and 7.30 (2 x brs, 2x4H, NH), 8.71 (s, 1H, Ar-H), one Ar-H resonance for the dinitrophenyl unit could not be located with certainty, it presumably overlaps the 7.02-7.13 signals. ^{13}C NMR (CD_2Cl_2, 500 MHz) δ: 27.7, 28.1, 28.5, 30.2, 30.4 (CH_3), 35.6, 45.0 (Cq), 103.3, 103.4, 103.7, 106.6, 120.1, 121.6, 125.1, 130.5 (CH), 134.5, 136.5, 138.8, 139.1, 139.8, 147.4, 152.1, 155.2 (Cq).

*Anti-anti-anti-***11.**

Anti-**5** (175 mg, 0.30 mmol) and Cs_2CO_3 (200 mg 0.6 mmol) were suspended in CH_3CN (50 ml) and refluxed under an Ar atmosphere for a few minutes, then cooled to room temperature before adding **9** (71 mg, 0.30 mmol) previously dissolved in CH_3CN (2 ml). The mixture was gently refluxed until the starting materials were no longer detectable (t.l.c. SiO_2, $PhCH_3$/EtOAc 8:2). Besides some (presumably polymeric) material that had negligible chromatographic mobility, one major component could be observed (R_f *ca*. 0.5 $PhCH_3$/EtOAc 8:2 and R_f *ca*. 0.3 DCM/$PhCH_3$ 8:2). The mixture was concentrated at reduced pressure (room temperature) and the residue was partitioned in DCM/water. The organic phase was concentrated and subjected to column chromatography (SiO_2, DCM/$PhCH_3$ 1:1, gradually replacing $PhCH_3$ with EtOAc). The main chromatographically mobile fraction (25 mg after solvent removal, *ca*. 4%, yellow-orange solid, 230-230 °C dec.) was characterised as *anti-anti-anti*-**11**: ^{1}H NMR (500 MHz, CD_2Cl_2) δ: 1.55 (brs, 36H and overlapping water, CH_3), 1.84 (s, 18H, CH_3), 5.71 and 5.91 (2 x brs, 2 x 12H, pyrrole β-CH), 6.59 (s, 3H, Ar-H), 6.91 and 7.11 (AA'BB' system, 2 x 12H, Ar-H), 7.17 (brs, 12H, NH), 8.82 (s, 3H, Ar-H). ^{13}C NMR (125 MHz, CD_2Cl_2) δ: 28.9, 29.3 (CH_3), 35.1, 44.5 (Cq), 103.3, 105.9, 118.5, 129.3 (CH) 135.9, 138.9, 152.4. Two CH (for the dinitrophenyl units) and three Cqs could not be located due to the low solubility of the sample. Calculated *m/z* for $C_{132}H_{120}N_{18}O_{18}$: 2244.9028 and for $C_{132}H_{120}N_{18}O_{18}Cl$: 2279.9028; found ESI-MS $[M-1]^-$: 2244.8855 and $[M+Cl]^-$: 2280.8730

*Syn-syn-syn-***11.**

Syn-**5** (200 mg, 0.34 mmol) and Cs_2CO_3 (112 mg 0.34 mmol) were suspended in CH_3CN (50 ml) and refluxed under an Ar atmosphere for a few minutes, then cooled to room temperature before adding **9** (83 mg, 0.34 mmol) previously dissolved in CH_3CN (2 ml). The mixture was gently refluxed until the starting materials were no longer detectable (t.l.c. SiO_2, $PhCH_3$/EtOAc 8:2). Besides some (presumably polymeric) material that had negligible chromatographic mobility, a number of fractions could be detected. The mixture was concentrated at reduced pressure (room temperature) and the residue was partitioned in DCM/water. The organic phase was concentrated and subjected to column chromatography (SiO_2, DCM). The main chromatographically mobile fraction just above the base-line on t.l.c. (SiO_2, DCM) could be isolated to give a powdery residue after solvent removal (10 mg, ca. 1.3%, yellow-orange solid) that was characterised as *syn-syn-syn*-**11**: ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.47, 1.61, 1.81 (3 x s, 3 x 18H, CH_3), 5.58 and 5.75 (2 x m, 2 x 12H, pyrrole β-CH), 6.59 (s, 3H, Ar-H), 6.91 and 7.04 (AA'BB' system, 2 x 12H, Ar-H), 6.95 (s, 3H, 3 x Ar-H), 8.93 (s, 3H, Ar-H), 9.56 (brs, 24, NH). ^{13}C NMR (125 MHz, CD_2Cl_2) δ: 30.7, 34.1 (CH_3), 43.6, 45.4 (Cq), 100.1, 102.7, 120.3, 129.3 (CH) 140.1, 156,1. Two CH and four Cq atoms could not be detected presumably due to very low solubility (a powder separated from DMSO solution during acquisition). Calculated *m/z* for $C_{132}H_{120}N_{18}O_{18}$: 2244.9028 and for $C_{132}H_{120}N_{18}O_{18}Cl$: 2279.9028; found ESI-MS $[M-1]^-$: 2244.8882 and $[M+Cl]^-$: 2280.8689.

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Supplementary Material

^{1}H and ^{13}C NMR spectra for the compounds **3**-**11** and related MS spectra.

References

1. Rothemund, P.; Gage, C. L. *J. Am. Chem. Soc.* **1955**, *77*, 3340-3342 and references therein. https://doi.org/10.1021/ja01617a056
2. Gale, P. A.; Sessler, J. L.; Kral, V.; Lynch, V. *J. Am. Chem. Soc.* **1996**, *118*, 5140-5141. https://doi.org/10.1021/ja960307r
3. Peng, S.; He, Q.; Vargas-Zuniga, G. I.; Qin, L.; Hwang, I.; Kim, S. K.; Heo, N. J.; Lee, C.-H.; Dutta, R.; Sessler, J. L. *Chem. Soc. Rev.* **2020**, *49*, 865-907. https://doi.org/10.1039/C9CS00528E
4. Rather, I. A.; Wagay, S. A.; Hasnain, M. S.; Ali, R. *RSC Adv.* **2019**, *9*, 38309-38344. http://dx.doi.org/10.1039/C9RA07399J
5. Saha, I.; Lee, J. T.; Lee, C.-H. *Eur. J. Org. Chem.* **2015**, 3859-3885. https://doi.org/10.1002/ejoc.201403701
6. Kim, D. S.; Sessler, J. L. *Chem. Soc. Rev.* **2015**, *44*, 532-546. https://doi.org/10.1039/C4CS00157E
7. Gale, P. A. *Acc. Chem. Res.* ***2011***, *44*, 216-226. https://doi.org/10.1021/ar100134p
8. Martinez-Crespo, L.; Sun-Wang, J. L.; Ferreira, P.; Mirabella, C. F. M.; Aragay, G.; Ballester, P. *Chem. - Eur. J.* **2019**, *25*, 4775-4781. https://doi.org/10.1002/chem.201806169
9. Guo, C.; Sedgwick, A. C.; Hirao, T.; Sessler, J. L. *Coord. Chem. Rev.* **2021**, *427*, 213560. https://doi.org/10.1016/j.ccr.2020.213560
10. Pushina, M.; Koutnik, P.; Nishiyabu, R.; Minami, T.; Savechenkov, P.; Anzenbacher, P., Jr. *Chem. - Eur. J.* **2018**, *24*, 4879-4884, and references therein. https://doi.org/10.1002/chem.201705387
11. Maeda, C.; Sasaki, S.; Takaishi, K.; Ema, T. *Catal. Sci. Technol.* **2018**, *8*, 4193-4198. https://doi.org/10.1039/C8CY00941D
12. Cafeo, G.; De Rosa, M.; Kohnke, F. H.; Soriente, A.; Talotta, C.; Valenti, L. *Molecules* **2009**, *14*, 2594-2601. https://doi.org/10.3390/molecules14072594
13. Cafeo, G.; De Rosa, M.; Kohnke, F. H.; Neri, P.; Soriente, A.; Valenti, L. *Tetrahedron Lett.* **2008**, *49*, 153-155. https://doi.org/10.1016/j.tetlet.2007.10.148
14. Kohnke, F. H. *Eur. J. Org. Chem.* **2020**, *2020*, 4261-4272, and references threin. https://doi.org/10.1002/ejoc.202000208

15. Jung, K.-B.; Kim, S. K.; Lynch, V. M.; Cho, D.-G.; Sessler, J. L. *Chem. Commun.* **2012**, *48*, 2495-7345.
http://dx.doi.org/10.1039/C2CC17888E
16. Sessler, J. L.; An, D.; Cho, W.-S.; Lynch, V.; Yoon, D.-W.; Hong, S.-J.; Lee, C.-H. *J. Org. Chem.* **2005***, 70,* 1511–1517.
https://doi.org/10.1021/jo048480q
17. Song, M. Y.; Na, H. K.; Kim, E. Y.; Lee, S. J.; Kim, K. I.; Baek, E. M.; Kim, H. S.; An, D. K.; Lee, C. H. *Tetrahedron Lett.* **2004**, *45*, 299-301.
https://doi.org/10.1016/j.tetlet.2003.10.170
18. Cafeo, G.; Kohnke, F. H.; La Torre, G. L.; Parisi, M. F.; Nascone, R. P.; White, A. J. P.; Williams, D. J. *Chem. - Eur. J.* **2002**, *8*, 3148-3156.
https://doi.org/10.1002/1521-3765(20020715)8:14%3C3148::AID-CHEM3148%3E3.0.CO;2-B
19. Rifai, A.; AlHaddad, N.; Noun, M.; Abbas, I.; Tabbal, M.; Shatila, R.; Cazier-Dennin, F.; Danjou, P.-E. *Org. Biomol. Chem.* **2019**, *17*, 5818-5825.
https://doi.org/10.1039/C9OB01106D
20. Kim, A.; Ali, R.; Park, S. H.; Kim, Y.-H.; Park, J. S. *Chem. Commun.* **2016**, *52*, 11139-11142.
http://dx.doi.org/10.1039/C6CC04562F
21. Kumar, C. D.; Sirisha, K.; Dhaked, D. K.; Lokesh, P.; Sarma, A. V. S.; Bharatam, P. V.; Kantevari, S.; Sripadi, P. *J. Org. Chem.* **2015**, *80*, 1746-1753.
https://doi.org/10.1021/jo502673c
22. Adriaenssens, L.; Gil-Ramirez, G.; Frontera, A.; Quinonero, D.; Escudero-Adan, E. C.; Ballester, P. *J. Am. Chem. Soc.* **2014**, *136*, 3208-3218.
https://doi.org/10.1021/ja412098v
23. Sokkalingam, P.; Kim, D. S.; Hwang, H.; Sessler, J. L.; Lee, C.-H. *Chem. Sci.* **2012**, *3*, 1819-1824.
https://doi.org/10.1039/C2SC20232H
24. Bruno, G.; Cafeo, G.; Kohnke, F. H.; Nicolo, F. *Tetrahedron* **2007**, *63*, 10003-10010.
https://doi.org/10.1016/j.tet.2007.07.060
25. Villarón, D.; Siegler, M. A.; Wezenberg, S. J. *Chem. Sci.* **2021***, 12,* 3188-3193, and references therein.
http://dx.doi.org/10.1039/D0SC06686A
26. Sekiya, R.; Diaz-Moscoso, A.; Ballester, P. *Chem. - Eur. J.* **2018**, *24*, 2182-2191.
https://doi.org/10.1002/chem.201704777
27. Cafeo, G.; Kohnke, F. H.; Mezzatesta, G.; Profumo, A.; Rosano, C.; Villari, A.; White, A. J. P. *Chem. - Eur. J.* **2015**, *21*, 5323-
https://doi.org/10.1002/chem.201406183
28. Lai, Z.; Zhao, T.; Sessler, J. L.; He, Q. *Coord. Chem. Rev.* **2020**, *425*, 213528.
https://doi.org/10.1016/j.ccr.2020.213528
29. He, Q.; Tu, P.; Sessler, J. L. *Chem* **2018**, *4*, 46-93 and references therein.
https://doi.org/10.1016/j.chempr.2017.10.015
30. He, Q.; Kelliher, M.; Bähring, S.; Lynch, V. M.; Sessler, J. L. *J. Am. Chem. Soc.* **2017**, *139*, 7140-7143.
https://doi.org/10.1021/jacs.7b02329
31. Galan, A.; Aragay, G.; Ballester, P. *Chem. Sci.* **2016***, 7,* 5976-5982.
https://doi.org/10.1039/C6SC01843B
32. Aydogan, A.; Akar, A. *Chem. - Eur. J.* **2012**, *18*, 1999-2005.
https://doi.org/10.1002/chem.201101605

33. Cafeo, G.; Gattuso, G.; Kohnke, F. H.; Papanikolaou, G.; Profumo, A.; Rosano, C. *Chem. - Eur. J.* **2014**, *20*, 1658-1668.
   http://dx.doi.org/10.1002/chem.201303265
34. Yoo, J.; Park, I.-w.; Kim, T.-Y.; Lee, C.-H. *Bull. Korean Chem. Soc.* **2010**, *31*, 630-634.
   https://doi.org/10.5012/bkcs.2010.31.03.630
35. Baxter, I.; Colquhoun, H. M.; Hodge, P.; Kohnke, F. H.; Lewis, D. F.; Williams, D. J. *J. Mater. Chem.* **2000**, *10*, 309-314.
   https://doi.org/10.1039/A908414B
36. Ben-Haida, A.; Baxter, I.; Colquhoun, H. M.; Hodge, P.; Kohnke, F. H.; Williams, D. J. *Chem. Commun.* **1997**, 1533.
   https://doi.org/10.1039/A703854B
37. Galan, A.; Escudero-Adan, E. C.; Frontera, A.; Ballester, P. *J. Org. Chem.* **2014**, *79*, 5545-5557.
   https://doi.org/10.1021/jo5007224
38. Takayama, Y.; Yamada, T.; Tatekabe, S.; Nagasawa, K. *Chem. Commun.* **2013**, *49*, 6519-6521.
   https://doi.org/10.1039/C3CC42463D
39. Ma, Y.-T.; Fan, H.-F.; Gao, Y.-Q.; Li, H.; Zhang, A.-L.; Gao, J.-M. *Chemical Biology & Drug Design* **2013**, *81*, 545-552.
   https://doi.org/10.1111/cbdd.12064
40. Han, Y.; Wang, G.-L.; Sun, J.-J.; Sun, J.; Yan, C.-G. *Tetrahedron* **2013**, *69*, 10604.[http://dx.doi.org/10.1016/j.tet.2013.10.036]