Abstract. We recently reported that DDQ-mediated oxidative coupling of pyrrole to a free-base meso-triarylcorrole in dichloromethane at room-temperature results in the near-instantaneous formation of pyrrole-appended isocorroles. Herein we report that the use of refluxing dichloromethane and longer reaction times results in the oxidative addition of a second molecule of pyrrole, affording a novel isoporphyrinoid macrocycle – calixcorrole – in up to 47% yield.

Contribution statement. SL and BCLP conducted all the experimental work, while AG coordinated the project. All authors contributed substantially to writing the manuscript.

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Introduction

Since the first report of an isoporphyrin by Dolphin over 50 years ago,¹ isoporphyrinoids have grown into a major class of compounds within the vast field of porphyrin analogues (the subject of a special issue of Chemical Reviews²). They are characterized by one or more saturated meso carbons, which interrupt or greatly diminish the global aromaticity of the macrocycle.³,⁴ Today, the isoporphyrinoids also include (in addition to isoporphyrins⁵,⁶) phlorins,⁷,⁸ porphyrinogens,⁹,¹⁰ calixpyrroles,¹¹ calixphyrins,¹²,¹³ and isocorroles¹⁴,¹⁵ as well as their expanded¹⁶,¹⁷ and N-confused derivatives¹⁸,¹⁹. The macrocycles are of interest for a variety of reasons, obviously as novel transition metal ligands,²⁰,²¹ but also as platforms for NIR dyes,²² molecular recognition²³ (especially anion sensing²⁴,²⁵), and drug delivery.²⁶ Herein, we wish to disclose the serendipitous discovery of new isoporphyrinoid – calixcorrole – the corrole analogue of calixphyrin.

![Synthesis of pyrrole-appended isocorrole and calixcorrole.](image)

Figure 1. Synthesis of pyrrole-appended isocorrole and calixcorrole.
Results and Discussion

(a) Detection and synthesis. While revisiting our recent ‘near-instantaneous’ synthesis of isocorroles\textsuperscript{27} via the DDQ-mediated oxidative coupling\textsuperscript{28,29,30,31} of pyrrole to corrole, we noticed a red fraction remaining on the column after column-chromatographic isolation of the isocorrole. Mass spectrometry indicated a molecular formula consistent with ‘corrole + 2pyrrole - 2H’, suggesting oxidative addition of a second molecule of pyrrole to the initially formed pyrrole-appended isocorrole, a surmise that \textsuperscript{1}H NMR spectroscopy would later confirm. We named the new product calixcorrole by analogy with calixphyrin.

We entertained two potential scenarios for calixcorrole formation, either as a result of longer reaction times at room temperature or through the action of heat during rotary evaporation of the reaction mixture. To test the alternatives, a small amount of meso-tris(2-methylphenyl)corrole, H\textsubscript{2}[TpMePC], was dissolved in dichloromethane, DDQ (2 eq) and pyrrole (10 eq) were added, and the reaction mixture was left to stir at room temperature. Periodic monitoring by ESI-MS over several hours revealed only isocorrole formation and no trace of calixcorrole. The latter promptly appeared on the MS, however, upon refluxing the mixture. With the importance of heating established, we scaled up the reaction to about 50 mg of corrole dissolved in \~20 mL dichloromethane and the same number of equivalents of DDQ and pyrrole as before. After refluxing overnight, chromatographic work-up led to the isolation of two fractions F1 and F2 of calixcorrole in 4.4 and 23.5\% yields, or a combined yield of 27.9\%. \textsuperscript{1}H NMR spectroscopy would later establish F1 and F2 as diastereomers.

The above synthesis of calixcorrole also led to a large quantity of pyrrole-appended isocorrole,\textsuperscript{27} abbreviated hereafter as H\textsubscript{2}[5/10-pyr-TpMePiC], suggesting to us that even longer reaction times would lead to higher yields of calixcorrole. Indeed, extending the reaction time to 5 days, keeping all other variables the same as above, led to combined yield of 38.8\% of the two fractions. Given the impracticality of a 5-day reaction, we then investigated higher-temperature reactions in THF and DMSO, but these resulted in isocorrole as the only observed product. Heating the corrole in toluene with 2-3 eq DDQ and 10-50 eq pyrrole to 100°C did result in calixcorrole (as evidenced by MS), but only in small amounts after several days of heating.

With dichloromethane emerging as the solvent of choice, we attempted to perform the reaction in a sealed vial under microwave irradiation, which allowed for the use of higher temperatures and pressures. Although a smaller-scale test reaction (\~10 mg corrole, 2 eq DDQ, and 40 eq pyrrole in dichloromethane) at 100 °C revealed calixcorrole as the main product after \~15 h, a subsequent normal-scale reaction (\~50 mg corrole, 2 eq DDQ, and 40 eq pyrrole in dichloromethane) at the same temperature yielded only a 15.3\% combined, isolated yield of calixcorrole. In the end, our best conditions for a normal-scale reaction consisted of refluxing \~50 mg of corrole in dichloromethane with 3 eq DDQ and 13 eq pyrrole for about 2
days. Following work-up, the isolated yields were 12.6 % for F1 and 34.0% for F2, corresponding to a combined yield of 46.6%.

(b) Spectroscopic characterization. 2D NMR spectroscopy, especially TOCSY and NOESY, established the constitution (regiochemistry) of the calixcorrole skeleton. However, the diastereomeric relationship of F1 and F2, i.e., their cisoid or transoid character, still remains unresolved. A cluster of broad singlets at ~8.0-8.4 ppm were assigned to the NH protons of the two appended pyrroles and the “isolated pyrrole” between the two saturated meso carbons. TOCSY cross-peaks identified the remaining protons of the appended pyrroles and the $\beta$-protons 12 and 13. Next, the 10- and 15-aryl protons were identified via their NOESY cross-peaks with the appended pyrrolyl protons. Additional NOESY cross-peaks of 10/15-aryl allowed the assignment of the adjacent $\beta$-protons 17 and 8. The remaining peaks were assigned by “tracing around the macrocycle” with NOESY and TOCSY.

Both calixcorrole isomers exhibit a lovely pinkish-red color, with a global visible $\lambda_{\text{max}}$ at 525 nm and a shoulder around 555 nm. In sharp contrast to pyrrole-appended isocorroles, they exhibit neither a Soret-like feature nor absorption in the near-infrared.

![Figure 2. Atom numbering used in $^1$H NMR assignments.](image-url)
Figure 3. $^1$H NMR spectrum of the major product F2.

Figure 4. $^1$H NMR spectrum of the minor product F1.
Figure 5. UV-vis spectra of calixcorrole diastereomers F1 and F2.

Figure 6. Comparative UV-vis-NIR spectra of calixcorrole diastereomers F1 and F2 and isocorrole H_2[5-pyr-TpMePiC].
Figure 7. High-res ESI MS spectrum of calixcorrole diastereomer F1.

Figure 8. High-res ESI MS spectrum of calixcorrole diastereomer F2.
Concluding remarks
In summary, we have described the serendipitous isolation a novel isoporphyrinoid – calixcorrole – via DDQ-mediated oxidative addition of two pyrrole molecules to meso-tris(p-methylphenyl)corrole. The product was obtained as two separable diastereomers with a combined yield of 46.6%. The molecular constitution (i.e., connectivity) was fully elucidated with 2D NMR analysis, but in the absence so far of a crystal structure (in spite of many attempts to obtain one and considerable experience with structure determination in the corrole field\textsuperscript{32,33,34,35}), the stereochemistry of the two diastereomers remains unresolved. Also, somewhat disappointingly, our preliminary attempts at metal insertion into calixcorrole have proved unsuccessful. Although copper appears to insert (as evidenced by MS),\textsuperscript{36} the complexes proved unstable and demetallated in the course of isolation. Gold also failed to insert via the ‘acetate method’.\textsuperscript{37} In spite of the setbacks, we view the discovery of calixcorrole as a significant development. The compound may lend itself to applications involving molecular recognition such as anion sensing and sugar sensing.\textsuperscript{38,39} Also, the synthetic strategy may prove useful elsewhere in porphyrin analogue chemistry, and help in the creation of new isoporphyrinoids with interesting and useful properties. Time will tell.

EXPERIMENTAL SECTION
Materials and instruments
All chemicals were obtained from Sigma-Aldrich (Merck) and used as such. Silica gel 60 (0.04–0.063 mm particle size; 230–400 mesh, Sigma) was used for column chromatography. UV-vis spectra were recorded on an HP 8454 spectrophotometer at room temperature. High-resolution electrospray ionization (ESI) mass spectra were recorded on an Orbitrap Exploris 120 (Figures 7 and 8). \textsuperscript{1}H NMR spectra were recorded on a Bruker Avance III HD 400 MHz spectrometer.

Synthesis of calixcorrole
To a solution of H\textsubscript{3}[TpMePC]\textsuperscript{40} (51.4 mg) and DDQ (61.8 mg, \~{}3 eq) in DCM (20 mL) was added pyrrole (0.82 mL, \~{}13 eq) and the resulting solution was brought to reflux. After 2 days at reflux the solvent was removed by rotary evaporation and the residue purified by silica column. DCM/n-hexane 1:3 eluted a small green fraction (isocorrole) after which the polarity was increased to DCM/n-hexane 1:1 to eluate a red/pink fraction corresponding to the calixcorroles as a mixture of diastereomers. The two diastereomers were separated via prep-TLC using DCM/n-hexane 1:2 to give 8.0 mg (12.6 %) of Calixcorrole F\textsubscript{1} and 21.5 mg (34 %) of Calixcorrole F\textsubscript{2}. Analytical details are as follows.
Calixcorrole F1: UV-Vis (CH₂Cl₂) λ_max (nm) [ε x 10⁴ (M⁻¹cm⁻¹)]: 231 (2.00), 295 (0.87), 361 (0.60), 398 (0.50), 525 (1.19). ¹H NMR (400 MHz, CDCl₃, δ): 13.66 (s, 1H, N3), 10.01 (s, 1H, N1), 8.18 (s, 1H, N2), 8.12 (s, 1H, 5-(2-pyrrrolyl NH)), 8.05 (s, 1H, 10-(2-pyrrrolyl NH)), 7.43 (d, J = 7.6 Hz, 2H, 15-o-Ph), 7.27 – 7.21 (m, 2H, 15-m-Ph), 7.17 – 7.06 (m, 6H, 10-m-Ph and 5-o/m-Ph), 7.00 (d, J = 8.0 Hz, 2H, 10-o-Ph), 6.87 (d, J = 4.4 Hz, 1H, 17), 6.71 – 6.65 (m, 3H, 18 and 10/5-(2-pyrrrolyl-a)), 6.58 – 6.52 (m, 1H, 2), 6.41 (d, J = 3.9 Hz, 1H, 13), 6.14 – 6.05 (m, 3H, 3 and 10/5-(2-pyrrrolyl-b)), 6.02 – 5.98 (m, 1H, 8), 5.98 – 5.95 (m, 1H, 5-(2-pyrrrolyl-c)), 5.91 – 5.84 (m, 2H, 12 and 10-(2-pyrrrolyl-c)), 5.79 – 5.73 (m, 1H, 7), 2.44 (s, 3H, 15-p-CH₃), 2.34 (s, 3H, 5-p-CH₃), 2.32 (s, 3H, 10-p-CH₃). MS (ESI) m/z: 701.3387; calcd for C₄₈H₄₀N₈H: 701.3387 [M + H⁺].

Calixcorrole F2: UV-Vis (CH₂Cl₂) λ_max (nm) [ε x 10⁴ (M⁻¹cm⁻¹)]: 231 (2.46), 297 (1.05), 361 (0.69), 398 (0.55), 524 (1.55). ¹H NMR (400 MHz, CDCl₃, δ): 13.73 (s, 1H, N3), 10.04 (s, 1H, N1), 8.36 (s, 1H, N2), 8.14 (s, 1H, 5-(2-pyrrrolyl NH)), 8.00 (s, 1H, 10-(2-pyrrrolyl NH)), 7.42 (d, J = 7.8 Hz, 2H, 15-o-Ph), 7.26 – 7.22 (m, 2H, 15-m-Ph), 7.12 (d, J = 8.4 Hz, 2H, 5-o-Ph), 7.09 – 7.00 (m, 6H, 10-o/m-Ph and 5-m-Ph), 6.87 (d, J = 4.4 Hz, 1H, 17), 6.73 – 6.70 (m, 2H, 10/5-(2-pyrrrolyl-a)), 6.69 (d, J = 4.5 Hz, 1H, 18), 6.56 (dd, J = 3.5, 2.5 Hz, 1H, 2), 6.40 (d, J = 3.9 Hz, 1H, 13), 6.24 – 6.14 (m, 2H, 10/5-(2-pyrrrolyl-b)), 6.12 – 6.03 (m, 2H, 3 and 5-(2-pyrrrolyl-c)), 5.98 – 5.95 (m, 1H, 10-(2-pyrrrolyl-c)), 5.94 (t, J = 3.1 Hz, 1H, 8), 5.86 (d, J = 3.9 Hz, 1H, 12), 5.75 (t, J = 3.0 Hz, 1H, 7), 2.44 (s, 3H, 15-p-CH₃), 2.33 (s, 3H, 5-p-CH₃), 2.31 (s, 3H, 10-p-CH₃). MS (ESI) m/z: 701.3385; calcd for C₄₈H₄₀N₈H: 701.3387 [M + H⁺].

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References