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A highly efficient preparation of *N*-confused cyclodecapyrroles

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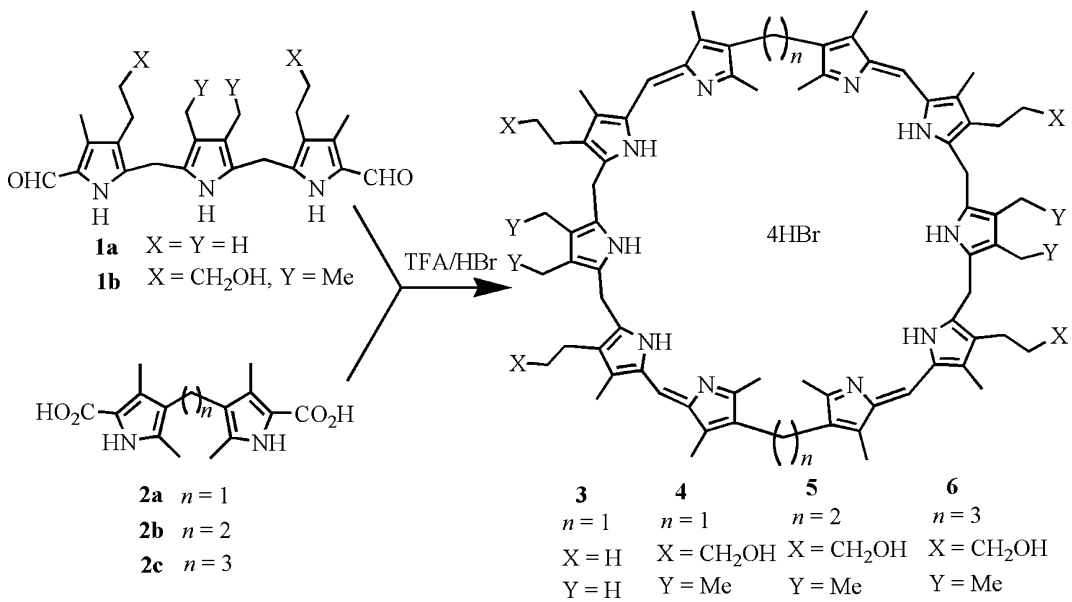
Abstract—Cyclodecapyrroles, potential novel host systems, were synthesized in 78–88% yields by condensation of tripyrrane dialdehyde with bis(5-carboxyl-2,4-dimethyl-pyrrole-3-yl)-methane, -ethane, and -propane in the presence of HBr and TFA.

Cyclopolypyrroles, such as fully conjugated expanded porphyrins, partially conjugated calixphyrins and non-conjugated calix[*n*]pyrroles, have recently received considerable attention due to the possibility to develop new chemistry,[1–3] the potential medical application as photosensitizers in photodynamic treatments of cancer, age-related macular degeneration, and atheromatous plaque,[4,5] and the intriguing properties such as selective anion[6,7] and neutral small molecule binding,[8] and forming bimetallic complexes.[9]

Cyclooctapyrroles,[6d,10] cyclodecapyrrole,[11] cyclododecapyrrole,[12,13] and cyclohexadecapyrrole[13] were usually synthesized by the 'MacDonald-type' condensation,[14] where a bipyrrole dialdehyde was condensed with a dipyrromethane,[6d,10,11] and terpyrrole[11] intermediates, or by the 'Rothemund reaction',[15] where a 5,5′-diunsubstituted 2,2′-bipyrrole was condensed with an aromatic aldehyde.[13] The yields were usually as low as 7–20%.[10–13] Herein, we report a simple high yield synthesis of cyclodecapyrrols (**3**–**6**, Scheme 1) through the 'Mac-



Scheme 1.

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Donald type' [3+2+3+2] condensation of tripyrrane dialdehyde **1** with 3,3′-dipyrrole intermediates **2**, that are to the best of our knowledge without precedent in the literature. These molecules, which contain *N*-confused pyrrole rings, and both sp^3-hybrodized bridging carbon atoms and *meso*-like dipyrromethene subunits, bear analogy to both calix[*n*]pyrrole[6–9] and the porphyrin/expanded porphyrin series of macrocycles,[1,2] and are potential novel host systems.

The synthesis of **3**–**6** is summarized in Scheme 1. Briefly, these compounds are prepared in good yields by the acid-catalyzed [3+2+3+2] condensation of tripyrrane dialdehyde **1**[16] with 3,3′-dipyrrole precursors **2**[17] at room temperature. Due to the limited solubility of 5,5′-dicarboxy-3,3′-dipyrrole **2**, it is first treated by trifluoroacetic acid at 40°C for 20 min to generate in situ the corresponding 5,5′-di-unsubstituted 3,3′-dipyrrole intermediates,[18] which smoothly condense at room temperature with tripyrranes **1** in a mixture of 50% dichloromethane and 50% methanol in the presence of strong acids such as hydrobromide in glacial acetic acid. After purification by precipitation from ether,[18] compounds **3**–**6** are obtained in yields of 78–88%.[19–22] Cyclodecapyrroles **3**–**6** are found to exist as their tetrahydrobromide salt forms. Extensive attempts to oxidize macrocycles **3** and **4** failed to give the corresponding fully conjugated systems by using a range of oxidation agents such as DDQ, $FeCl_3$, $(NH_4)_2Ce(NO_3)_6$, $Pb(OAc)_4$, Br_2, etc. in different solvents such as THF, THF–H_2O, acetic acid, trifluoroacetic acid, dichloromethane–methanol, etc. We assume that the presence of the β,β-CH_2-bridges makes the macrocycles less susceptible to oxidation.

The constitutional structures of **3**–**6** followed the structures of their starting materials tripyrrane dialdehyde **1** and 5,5-dicarboxy-3,3′-dipyrrole **2**, and were confirmed by their mass spectrometry, proton NMR spectra, and combustion analysis. All mass spectra of **3**–**6** give the expected molecular weight, which is consistent with the [3+2+3+2] 'MacDonald type' condensation products. The proton spectra show the macrocycles are symmetric, which exhibit a characteristic singlet for *meso*-CH= at 7.00–7.15 ppm and a singlet for *meso*-CH_2- bridges at 3.40–3.50 ppm. The signals of NH protons are observed at 9–10 ppm. Cyclodecapyrroles **3**–**6** are noticeably orange-red, and their long wavelength bands are observed at 495–505 nm in dichloromethane, which are thus bathochromically shifted with respect to dipyrromethene hydrochloride salt (475 nm).[23] Combustion analyses suggest cyclodecapyrroles **3**–**6** exist as the corresponding tetrahydrobromide salts. UV–vis studies show that **3**–**6**, like dipyrromethenes,[24] are gradually decomposed in basic solution such as in dichloromethane containing a drop of triethylamine, which suggest the macrocycles are not stable in their free base forms. Accordingly, we recommend converting the macrocycles into their tetrahydrobromide salt forms, which are stable at room temperature for more than 2 years without noticeable decomposition.

Transition metal ions Zn(II), Fe(II), Ni(II), and Cu(II) are observed to form complexes with cyclodecapyrroles **3**–**6** in dichloromethane. However, as exemplified with a series of absorption spectra of solutions with varying relative amounts of ligand and Zn(II) ions, there seems to exist a complicated cascade of different complexes. Therefore, the nature of these complexes could not be derived.

In summary, a high yield preparation of cyclodecapyrroles **3**–**6**, containing *N*-confused pyrrole rings, are reported. Their anion or neutral small molecule binding ability is currently under study.

Acknowledgements

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18. *General procedure for the synthesis of* ***3–6***. 5,5′-Dicarboxy-3,3′-dipyrrole **2** (200 mg, 0.69 mmol) was suspended in trifluoroacetic acid (10 mL), and stirred at 40°C for 20 min. The red mixture was cooled down to room temperature. Tripyrrane dialdehydes **3** (252 mg, 0.69 mmol, 1.0 equiv.) was then added at once under continuous stirring. After 10 min, a mixture of dichloromethane (20 mL), methanol (20 mL) and hydrogen bromide (3 mL, 48% in acetic acid) was added. The red mixture was allowed to stir for 2 h at room temperature. Anhydrous ether (100 mL) was added and the suspension solution was allowed to stir for another 30 min. The red solid was collected by suction filtration and washed by anhydrous ether. The crude product was suspended in methanol (50 mL) and stirred for 30 min. The solid was collected by filtration. The crude product was dissolved in a minimum amount of trifluoroacetic acid (~5 mL) and dichloromethane (5 mL), and then hydrogen bromide (five drops, 48% in acetic acid) and methanol (5 mL) were added, followed by anhydrous ether to precipitate the product. The red solid was collected by centrifuge and dissolved in a minimum amount of TFA and the above procedure was repeated twice. Pure product was obtained as a red solid.
19. Cyclodecapyrrole **3**·4HBr: Yield 85%. Mp 285°C (dec.). ^{1}H NMR ($CDCl_3$/TFA-*d*, 9/1, v/v, 200 MHz), $\delta=0.85$ (t, $J=7.32$ Hz, 12H, 4C***H***$_3$), 1.80 (m, 18H, 6C***H***$_3$), 2.20–2.60 (m, 38H, 10***CH***$_3$, 4C***H***$_2$), 3.50 (s, 4H, 2C***H***$_2$), 7.00 (s, 4H, 4-C***H***=), 9.00 (s, 2H, 2N***H***), 10.20 (br s, 8H, 8N***H***) ppm. MS (LISMS): m/e = 1120 (M^+–4HBr). HRMS (LISMS, matrix:thioglycerol+$CHCl_3$), for $C_{74}H_{90}N_{10}$, required: 1119.74282, found: 1119.74297. UV–vis (CH_2Cl_2): $\lambda_{max}(\varepsilon)=505$ (57 300), 369 (27 100) nm. UV–vis (DMSO): $\lambda_{max}(\varepsilon)=495$ (69 800), 450^{sh} (54 400), 371 (33 300) nm.
20. Cyclodecapyrrole **4**·4HBr: Yield: 83%. Mp 295°C (dec.). ^{1}H NMR ($CDCl_3$/TFA-*d*, 9/1, v/v, 200 MHz), $\delta=0.85$ (t, $J=7.32$ Hz, 12H, 4CH_3), 1.15 (br s, 8H, 4CH_2), 1.95 (s, 12H, 4CH_3), 2.00–2.10 (m, 40H, 8CH_3, 8CH_2), 2.80 (s, 4H, 2CH_2), 2.95 (s, 8H, 4CH_2), 3.50 (br s, 8H, 4CH_2O), 6.80 (s, 4H, 4-CH=), 9.00 (br s, 4H, 4N***H***), 11.20 (6H, obscured by TFA-D, 6N***H***) ppm. MS (LSIMS, matrix:thioglycerol): m/e = 1392, 1295 (M^++1–4HBr). UV–vis (CH_2Cl_2): $\lambda_{max}(\varepsilon)=505$ (91 200) nm. UV–vis (DMSO): $\lambda_{max}(\varepsilon)=509$ (100 400) nm. Calcd for $C_{82}H_{106}N_{10}O_4$·4HBr·H_2O: C, 60.00; H, 7.12; N, 8.53. Found: C, 60.18; H, 7.10; N, 7.78.
21. Cyclodecapyrrole **5**·4HBr: Yield: 88%. Mp 298°C (dec.). ^{1}H NMR ($CDCl_3$/TFA-*d*/MeOH-d_4, 8/1/1, v/v, 200 MHz), $\delta=0.85$ (br s, 12H, 4CH_2C***H***$_3$), 1.20 (m, 8H, 4C***H***$_2$), 2.01 (s, 12H, 4C***H***$_3$), 2.20 (m, 40H, 8CH_2, 8CH_3), 2.60 (br s, 8H, 4C***H***$_2$), 3.40 (s, 8H, 4C***H***$_2$), 4.20 (s, 8H, 4CH_2), 7.10 (s, 4H, 4-C***H***=) ppm. MS(TOF MS): 1405.8 (M^++HBr), 1324 (M^++1). UV–vis (CH_2Cl_2): $\lambda_{max}(\varepsilon)=496$ (138 000) nm. UV–vis (DMSO): $\lambda_{max}(\varepsilon)=508$ (153 400) nm. Calcd for $C_{84}H_{110}N_{10}O_4$·4HBr·H_2O: C, 60.58; H, 7.02; N, 8.41. Found: C, 60.56; H, 6.94; N, 8.10.
22. Cyclodecapyrrole **6**·4HBr: Yield: 78%. Mp 280°C (dec.). ^{1}H NMR ($CDCl_3$/TFA-*d*/MeOH-d_4, 8/1/1, v/v, 200 MHz), $\delta=1.00$ (br s, 12H, 4C***H***$_3$), 1.20 (br s, 8H, 4C***H***$_2$), 2.20 (m, 32H, 8C***H***$_3$, 4C***H***$_2$), 2.40 (m, H, 4CH_3, 12C***H***$_2$), 3.50 (br s, 8H, 4C***H***$_2$), 4.20 (br s, 8H, 4C***H***$_2$), 7.10 (s, 4H, 4-C***H***=) ppm. MS (TOF): 1351.9 (M^++1–4HBr), 676.5 (1/2M^+), 451.7. UV–vis (CH_2Cl_2): $\lambda_{max}(\varepsilon)=500$ (127 700) nm. UV–vis (DMSO): $\lambda_{max}(\varepsilon)=496$ (122 200) nm. Calcd for $C_{86}H_{114}N_{10}O_4$·4HBr·H_2O, C, 60.99; H, 7.14; N, 8.27. Found: C, 60.66; H, 6.96; N, 8.20.
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