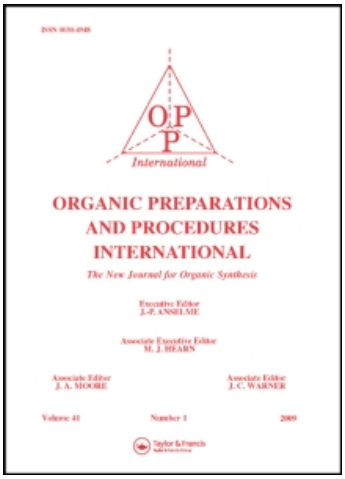

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SYNTHESIS OF NOVEL TETRAPYRROLES AND THEIR ZINC COMPLEXES

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SYNTHESIS OF NOVEL TETRAPYRROLES AND THEIR ZINC COMPLEXES

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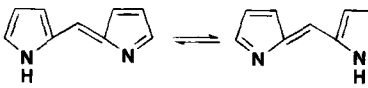
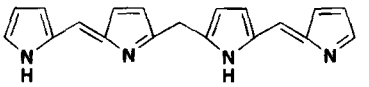
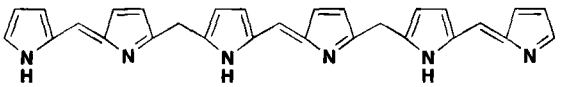
Self-assembling coordination complexes from suitable ligands and metal ions are of current interest to chemists. Among many ligands designed, dipyrrins **1** were recently found to be ideal building blocks for supramolecular assemblies.[1,2] Dipyrrins **1**, formerly called dipyrromethenes, are yellow colored, fully conjugated flat molecules containing 10 π-electrons, which are important building blocks for porphyrins, bile pigments, and linear polypyrroles.[3,4] The NH hydrogen of dipyrrin **1** can be removed to give a monoanionic species which is a resonance stabilized ligand. Since the complexes generated by dipyrrins **1** and metal ions are neutral species, counterions are not needed. Consequently, it is particularly convenient to purify the complexes by column chromatography.[1,2] That is in contrast to the polybipyrridine ligands,[5-9] in which anions as counterions are required when they react with metal ions.



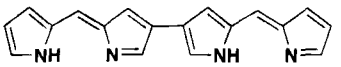
1 Dipyrrin



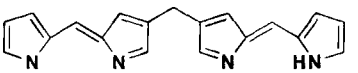
2 Biladiene-ac



3 Hexapyrrin



4 3,3'-Bidipyrrin

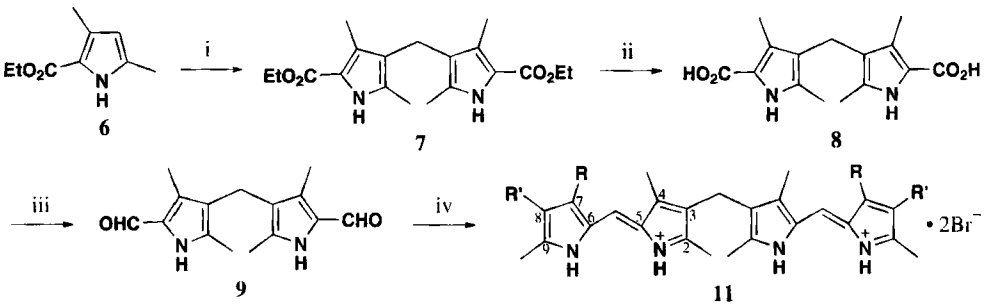


5 3,3'-Bisdipyrrinylmethane

Self-assemblies of polydipyrrins such as biladiene-ac **2**,[1] hexapyrrins **3**[1] and 3,3'-bidipyrrins **4**[2] have been reported. The triangle-shaped macrocyclic trimer[2] from the coordination of **4** with zinc (II) is particularly interesting. The brief synthesis and self-assembly of **5** with zinc(II) were reported[10,11] recently; the X-ray analysis of its double-stranded assembly of **5** with zinc(II) was also described. Dolphin *et al.*[11] provided a successful analysis of two diastereomeric helical complexes of

5 with zinc (II) by ^{1}H NMR spectroscopy, and an alternative procedure in detail.[12] Two dipyrrin units in compound **5** are separated by a -CH_2- bridge at 3,3'-positions and the rotation around the -CH_2- bridge is possible. Therefore, the pattern of self-assembly of compound **5** is different from that of compound **4**. Herein we report a new approach to 3,3'-linked dipyrrin spaced by methylene group, and the synthesis and self-assembly of compound **11**.

The novel tetrapyrrole ligands **11** were synthesized in four steps in overall yield about 39% starting from 3-unsubstituted pyrrole **6** as shown in *Scheme 1* [the condensation of **9** with **10** proceeds with loss of CO_2R (R = H, *t*-Bu) in the presence of TFA]. Although 2,2'-dipyrromethanes have been long known and extensively used to synthesize a variety of porphyrins, macrocycles related to porphyrins, linear polypyrroles and bile pigments,[3,4] 3,3'-dipyrromethanes **7** have been less explored. To the best of our knowledge, there were only a few examples reported in the literature,[13,14] albeit without detailed synthetic procedures and proper characterization. Fischer *et al.* obtained these compounds by coupling β-unsubstituted monopyrroles in formaldehyde solution in the presence of acid.[15] We have also developed an efficient method by which the key intermediate 3,3'-dipyrromethane **7** was prepared in high yield by coupling 2-ethoxycarbonyl-3,5-dimethylpyrrole (**6**)[16] with paraformaldehyde in hydrogen chloride-glacial acetic acid at room temperature. It is worth noting that if the same reaction was run below 0°, the unsubstituted position of pyrrole **6** was chloromethylated to yield 2-ethoxycarbonyl-4-(chloromethyl)-3,5-dimethylpyrrole.[17] The purification of compound **7** was particularly convenient since it precipitated out during the reaction and could be collected by simple filtration.



a) R = CH_3, R' = C_2H_5, R" = t-Bu
b) R = C_2H_5, R' = C_2H_5, R" = H
c) R = CH_3, R' = $(CH_2)_2CO_2CH_3$, R" = H

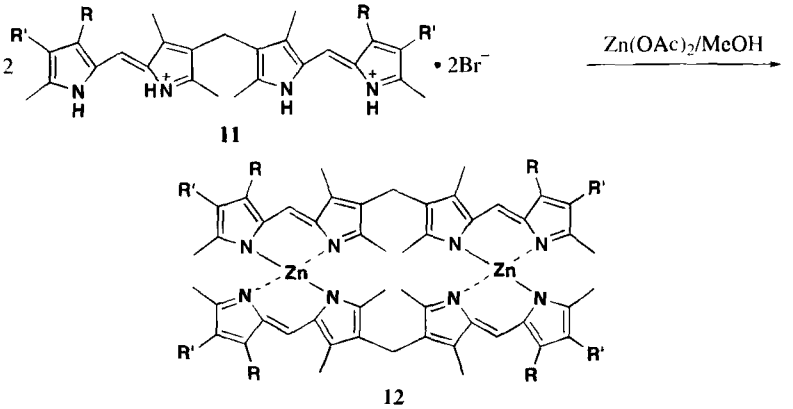
i) $(CH_2O)_n$, HCl, HOAc, r.t. ii) NaOH/heat, then H^+
iii) DMF/heat, benzoyl chloride, then Na_2CO_3-H_2O
iv) CH_3OH and Compound **10** in TFA, HBr-HOAc

Scheme 1

Unlike the 2,2'-dipyrromethane analogs,[18] saponification of **7** using large excess amount of sodium hydroxide (4 mole equiv.) in aqueous ethanol under reflux for 5h afforded the diacid **8** (quantitative yield) which was further converted to the corresponding diformyl intermediate **9** according to a modification of a *Vilsmeier-Haack* formylation procedure.[19] Condensation of **9** with 2-

carboxypyrroles or the corresponding *tert*-butyl ester pyrrole **10**[20] with trifluoroacetic acid generated the expected tetrapyrrole **11** in high yields.

When a solution of $Zn(OAc)_2$ in MeOH was added to a solution of **11** in $CHCl_3$, complexes **12** formed in greater than 90% yields. They are dimeric complexes with a ligand:metal ratio of 2:2 confirmed by MALDI-TOF mass spectroscopy. The X-ray structure[10] of zinc complex of **11a** shows that it has double stranded helical geometry, resulting from a twist around the $-CH_2-$ bridge in **11**.



Scheme 2

In summary, our work has provided an efficient route to 3,3'-linked dipyrrins, which are very useful building blocks to helical supramolecular architectures.

EXPERIMENTAL SECTION

Mass spectra were measured on Brucker APEX II and KYKY-ZHP-5 instruments. All NMR spectra (δ downfield from internal TMS) were run on a Varian Unity 200 spectrometer. All solvents and reagents were purchased from Beijing Chemical Factory, Beijing. The solvents and liquid reagents were distilled before use. UV-vis absorption spectra were run on a Hitachi U-2001 spectrophotometer. Elemental analyses were measured on a Carlo Erba-1106 instrument. The starting compounds 3,5-dimethyl-2-ethoxycarbonyl-1H-pyrrole **6**,[16] 3,5-dimethyl-4-ethyl-2-t-butoxycarbonyl-1H-pyrrole **10a**,[20] 3,4-diethyl-5-methyl-1H-pyrrole-2-carboxyl acid **10b**[21] and 3,5-dimethyl-2-carboxy-1H-pyrrole-4-propanoic acid **10c**[18] were synthesized according to the literature.

2,2',4,4'-Tetramethyl-5,5'-diethoxycarbonyl-3,3'-dipyrromethane (7).- To a solution of 3,5-dimethyl-2-ethoxycarbonyl-1H-pyrrole (15 g, 89.7 mmol) in 100 mL acetic acid, was added (2 g, 66.7 mmol based on CH_2O) paraformaldehyde. The mixture was stirred at room temperature while dry hydrogen chloride was passed through. After 4 hours, the reaction was stopped and the mixture was kept overnight. The product was collected and washed with ether to give 12.9 g (83%) pure dipyrromethane (**7**) as a colorless solid mp. 236-238°. EI-MS: m/e 346; UV-VIS: $\lambda_{max}(CH_2Cl_2)$ 283nm (ε 36,100); ^1H NMR (200MHz, $CDCl_3$): δ 1.34 (t, 6H, CH_3), 2.05 (s, 6H, CH_3), 2.17 (s, 6H, CH_3), 3.46 (s, 2H, CH_2), 4.28 (q, 4H, CH_2), 8.73 (s, 2H, NH); ^{13}C NMR (50MHz, $CDCl_3$): δ 10.60,

11.13, 19.03, 58.79, 115.73, 119.25, 126.16, 130.47, 160.95.

Anal. Calcd. For $C_{19}H_{26}N_2O_4$: C, 65.87; H, 7.56; N, 8.09. Found: C, 65.88; H, 7.38; N, 7.85

2,2',4,4'-Tetramethyldipyrromethane-5,5'-dicarboxylic Acid (8).- 2,2',4,4'-Tetramethyl-5,5'-diethoxycarbonyl-3,3'-dipyrromethane (2g, 5.8 mmol) and sodium hydroxide (1g, 25.0 mmol) were suspended in 20 mL 95% ethanol, and 5 mL water was added. The mixture was refluxed for 5 hours. After ethanol was removed under reduced pressure, the solution was poured into 200 mL ice water and was neutralized with 1N sulfuric acid to pH 6. The white precipitate was collected and dried under vacuum to give 1.4g (84%) of colorless solid, mp. 128-130°; ^{1}H NMR (200MHz, DMSO-d_6): δ 1.90 (s, 6H, CH_3), 2.10 (s, 6H, CH_3), 3.20 (s, 2H, CH_2), 10.95 (s, 4H, 2COOH, 2NH); ^{13}C NMR (50MHz, DMSO-d_6): δ 11.20, 11.34, 19.50, 121.33, 127.67, 130.32, 136.43, 161.55.

Anal. Calcd For $C_{15}H_{18}N_2O_4$: C, 62.06; H, 6.25; N, 9.65. Found: C, 61.88; H, 6.31; N, 9.46

2,2',4,4'-Tetramethyl-5,5'-diformyl-3,3'-dipyrromethane (9).- 2,2',4,4'-Tetramethyl-dipyrromethane-5,5'-dicarboxylic acid (2.2 g, 7.6 mmol) was dissolved in 15 mL dry N,N-dimethyl-formamide. The mixture was refluxed for 30 minutes under nitrogen and then cooled to 0° and maintained at this temperature while benzoyl chloride (3.5 mL) was added dropwise while stirring. After 20 min dry benzene 20 mL was added and the mixture was stirred at room temperature for 1 hour. The precipitate was collected and washed with benzene. The solid was added to 50 mL aqueous ethanol (50%) containing 3.5 g sodium carbonate. The mixture was refluxed for 10 min and then 40 mL water was added. After stirred for 2 hours at room temperature the product was collected and recrystallized from ethanol to give 1.5 g of **9** (77%) as a yellow solid, mp. > 250°; EI-MS: m/e 258; UV-VIS: λ_{max} (DMSO) 314 nm (ε 29,600); ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.04 (s, 6H, CH_3), 2.09 (s, 6H, CH_3), 3.39 (s, 2H, CH_2), 9.40 (s, 2H, CHO), 11.43 (s, 2H, NH); ^{13}C NMR (50MHz, DMSO-d_6): δ 8.91, 11.34, 18.42, 119.92, 127.54, 130.70, 135.17, 175.83.

Anal. Calcd For $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.63; H, 7.04; N, 10.71

General Procedure for Synthesis of 11.- A solution of **10** (3.8 mmol) in 5 mL trifluoroacetic acid was stirred at room temperature for 10 min, then a solution of 2,2',4,4'-tetramethyl-5,5'-diformyl-3,3'-dipyrromethane **9** (0.5 g, 1.9 mmol) in 10 mL trifluoroacetic acid and 10 mL methanol were added, followed by 10 mL HBr-HOAc (45%). The mixture was stirred for 2 hr, and 50 mL of ether was added. The solid was collected and recrystalized from methanol-acetone.

***bis*(2,4,7,9-Tetramethyl-8-ethyldipyrrin-3-yl)methane (11a)**, an orange solid, mp. > 250° (dec.), 73% yield; FAB-MS: M+1 469; UV-VIS: λ_{max} (CH_2Cl_2) 504nm (ε 316,900), 461nm (ε 98,400); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.08 (t, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.44 (q, 2H, CH_2), 2.57 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 3.57 (s, 2H, CH_2), 7.04 (s, 2H, -CH=), 13.07 (s, 1H, NH), 13.16 (s, 1H, NH); ^{13}C NMR (50Hz, $CDCl_3$): δ 9.99, 10.36, 12.90, 14.30, 17.16, 19.47, 118.82, 124.32, 125.43, 126.76, 131.34, 140.84, 142.34, 151.89, 155.97.

Anal. Calcd For $C_{31}H_{42}Br_2N_4$: C, 59.05; H, 6.71; N, 8.89. Found: C, 58.83; H, 6.68; N, 8.87

***bis*(2,4,9-Trimethyl-7,8-diethyldipyrrin-3-yl)methane (11b)**, an orange solid, mp. > 250° (dec.), 72% yield; FAB-MS: M+1 497; UV-VIS: λ_{max} (CH_2Cl_2) 504nm (ε 198,900), 461nm (ε 59,100); ^{1}H

NMR (200 MHz, $CDCl_3$): δ 1.11 (t, 6H, CH_3), 1.21 (t, 6H, CH_3), 2.14 (s, 6H, CH_3), 2.41 (q, 4H, CH_2), 2.59 (s, 6H, CH_3), 2.64 (q, 4H, CH_2), 2.70 (s, 6H, CH_3), 3.57 (s, 2H, CH_2), 7.02 (s, 2H, -CH=), 7.02 (s, 2H, -CH=), 13.04 (s, 1H, NH), 13.11 (s, 1H, NH); ^{13}C NMR (50Hz, $CDCl_3$): δ 10.34, 12.89, 14.77, 17.01, 18.05, 19.37, 118.61, 124.31, 125.47, 125.73, 130.59, 140.84, 148.69, 151.87, 156.16.

Anal. Calcd For $C_{33}H_{46}Br_2N_4$: C, 60.19; H, 7.04; N, 8.51. Found: C, 59.91; H, 7.04; N, 8.36

***bis*(2,4,9-Tetramethyl-7-methoxycarbonylethyl-8-ethyldipyrrin-3-yl)methane (11c)**, an orange solid, mp. > 250° (dec.), 69% yield; FAB-MS: M+1 585; UV-VIS: λ_{max} (CH_2Cl_2) 504nm (ε 192,600), 461nm (ε 58,200); ^1H NMR (200 MHz, $CDCl_3$): δ 2.16 (s, 6H, CH_3), 2.31 (s, 6H, CH_3), 2.47 (t, 4H, CH_2), 2.58 (s, 6H, CH_3), 2.70 (s, 6H, CH_3), 2.72 (t, 4H, CH_2), 3.58 (s, 2H, CH_2), 3.57 (s, 6H, CH_3), 7.06 (s, 2H, -CH=), 13.19 (s, 1H, NH), 13.20 (s, 1H, NH); ^{13}C NMR (50Hz, $CDCl_3$): δ 10.13, 10.33, 12.84, 19.16, 19.40, 51.89, 119.15, 124.55, 125.55, 126.44, 127.28, 141.44, 142.98, 152.89, 155.28, 172.50.

Anal. Calcd For $C_{35}H_{46}Br_2N_4O_4$: C, 56.31; H, 6.21; N, 7.50. Found: C, 56.16; H, 6.34; N, 7.67

General Procedure for the Synthesis of Complexes 12.- To a 20 mL solution of 0.24 mmol of tetrapyrrole **11** in chloroform was added a solution of 15 mL of 0.08 g zinc acetate dihydrate and 0.03 g sodium acetate in methanol. The mixture was stirred for 1 hr, then the solvent was concentrated to 20 mL. The precipitate was collected and washed with methanol and crystallized from $CHCl_3$-CH_3OH as red needles.

Zinc Complex 12a: mp. > 250° (dec.); MALDI-TOF-MS:1060; UV-VIS: λ_{max} (CH_2Cl_2) 527 nm (ε 326,700), 478 nm (ε 130,000); ^1H NMR (200 MHz, $CDCl_3$): δ 1.01 (t, 12H,CH_3), 1.38 (s, 12H, CH_3), 1.99 (s, 12H, CH_3), 2.19 (s, 12H, CH_3), 2.20 (s, 12H, CH_3), 2.34 (q, 8H, CH_2), 3.40 (s, 4H, CH_2), 6.87 (s, 4H, -CH=); ^{13}C NMR (50MHz, $CDCl_3$): δ 9.86, 14.90, 15.10, 17.97, 20.47, 120.28, 125.55, 129.19, 135.06, 135.26, 136.01, 136.31, 155.79, 157.16.

Anal. Calcd For $C_{62}H_{76}N_8Zn_2 \cdot H_2O$: C, 68,82; H, 7.27; N, 10.36. Found: C, 68.86; H, 7.21; N, 10.30

Zinc Complex 12c: mp. > 250° (dec.); MALDI-TOF-MS:1292; UV-VIS: λ_{max} (CH_2Cl_2) 526 nm (ε 324,000), 477 nm (ε 126,700); ^1H NMR (200 MHz, $CDCl_3$): δ 1.38 (s, 12H, CH_3), 1.97 (s, 12H, CH_3), 2.20 (s, 24H, CH_3), 2.39 (t, 8H, CH_2), 2.69 (t, 8H, CH_2), 3.40 (s, 4H, CH_2), 3.63 (s, 12H, CH_3), 6.88 (s, 4H, -CH=); ^{13}C NMR (50MHz, $CDCl_3$): δ 9.86, 14.76, 14.95, 20.40, 34.86, 51.44, 120.62, 124.96, 126.10, 135.04, 135.48, 136.74, 136.92, 154.92, 156.15, 173.62.

Anal. Calcd For $C_{70}H_{84}N_8O_8Zn_2 \cdot H_2O$: C, 63.97; H, 6.59; N, 8.53. Found: C, 63.98; H, 6.40; N, 8.26

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