Novel Synthesis of Phlorin Derivatives and Their Anion Binding Properties  
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Phlorins are one of the intermediate structures between calix[4]pyrrole and porphyrin. Phlorins bearing one sp3  
hybridized meso-carbon have been known to be unstable and only a few have been characterized so far.1 Compounds  
bearing meso-hydrogens are known to be especially unstable. Due to air sensitive nature of the compound,  
briding unit between N(21) and N(22) or N-substituents were introduced in some cases for the stabilization of the  
compounds.2 We recently reported the synthesis of phlorin 2 via oxidant-mediated coupling of pentapyrrotetramethane  
which was easily converted to the corresponding porphyrin under strongly acidic conditions.3  

\[
\begin{align*}  
1 & \quad \text{DDQ} \\
\text{Ph} & \quad \text{H} \\
\text{Ph} & \quad \text{H}
\end{align*}
\]

The fully meso-oxidized macrocycles, porphyrins are cation coordinating while the reduced porphyrin analogues  
have been recognized as anion receptors.4 Especially calix[4]-pyrroles have been extensively studied as easily accessible  
anion receptors. But, anion binding chemistry for stable phlorin analogues such as 2, 3 and 4 has not been studied  
well so far and thus here we report the novel ‘2+2’ type synthesis of stable phlorin derivatives and their anion  
binding behaviour in organic solvents.  

Sessler et al. reported an attempted synthesis of compound 4 by acid catalyzed condensation of tetrapyrrorotetramethane  
(linear tetrpyrrolic oligomer) with acetone, resulting unexpected isolation of meso-hydroxylated calixpyrarin.5  
Our approaches for the synthesis of compound 3 and 4 are shown in Scheme 1. Dipyrromethanes 5 and 6 were easily  
synthesized by acid-catalyzed condensation of corresponding ketone with pyrrole. Pyrrole was used as solvent as well as a  
reactant in these reactions. The product was easily isolated by vacuum distillation.6  

The condensation of acetone with pyrrole afforded meso-dimethyldipyrrormethane 6 in 60% yield while condensation  
of the benzophenone with pyrrole gave lower (12%) yield of 5. Then diol 7 synthesized as previously reported procedure7  
was used as southern half of the expected product. Treatment of 7 with 5 in acetonitrile in the presence of BF3, followed by  
DDQ oxidation and column chromatography of the resulting mixture afforded 3 in 2% yield. Similar condensation of 7  
with 6 under the same condition did not afford the desired product but polymeric material and small amount of TPP.  
Mixed condensation of meso-dimethylidipyrrormethane 6, benzaldehyde and meso-phenyldipyrrormethane 8, followed by  
DDQ oxidation afforded mixture of products 9, 10, and 11 in 9%, 1% and 4% respectively (Scheme 2).  

The formation of 9 and 11 is easily predicted and the reaction did not afford the cross-condensation product (i.e.  

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\begin{align*}  
5, R_1 = R_2 = \text{Ph} \\
6, R_1 = R_2 = \text{Methyl}
\end{align*}
\]

\[
\begin{align*}  
7 & \quad \text{CH3CN} \\
\text{CH3CN} & \quad \text{BDQ} 3
\end{align*}
\]

\[
\begin{align*}  
\text{Ph} & \quad \text{H} \\
\text{Ph} & \quad \text{H} \\
\text{Ph} & \quad \text{H} \\
\text{Ph} & \quad \text{H}
\end{align*}
\]

\[
\begin{align*}  
\text{Ph} & \quad \text{H} \\
\text{Ph} & \quad \text{H} \\
\text{Ph} & \quad \text{H} \\
\text{Ph} & \quad \text{H}
\end{align*}
\]

\[
\begin{align*}  
\text{Ph} & \quad \text{H} \\
\text{Ph} & \quad \text{H} \\
\text{Ph} & \quad \text{H} \\
\text{Ph} & \quad \text{H}
\end{align*}
\]

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\begin{align*}  
\text{Ph} & \quad \text{H} \\
\text{Ph} & \quad \text{H} \\
\text{Ph} & \quad \text{H} \\
\text{Ph} & \quad \text{H}
\end{align*}
\]

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\begin{align*}  
\text{Ph} & \quad \text{H} \\
\text{Ph} & \quad \text{H} \\
\text{Ph} & \quad \text{H} \\
\text{Ph} & \quad \text{H}
\end{align*}
\]
condensation of 6, 8 and two molecules of benzaldehyde. The formation of oxophlorin 10 is rather unusual on the other hand and considered to be formed by elimination of phenyl group from 8 followed by condensation with benzaldehyde and consecutive oxidation of meso-position. The compound 9 shows a single pyrrolic N-H resonance at 14.10 ppm which indicates the existence of strong intra-molecular hydrogen bonding. The proton NMR spectrum of 10 reveals the presence of single N-H resonance at -1.68 ppm. UV-Vis spectrum of 10 shows typical porphyrin-like absorption (Soret at 409 nm, Q band at 505 nm, 539 nm, 569 nm and 619 nm) and IR spectrum shows a typical carbonyl-stretching band of oxophlorin at 1560 cm\(^{-1}\) indicating the compound exist as keto-form.\(^8\)

The ability of the meso-pyrrylphlorin 2 in binding with fluoride anion was investigated using UV-Vis spectroscopy. As shown in Figure 1, the solution of 2 undergoes dramatic color changes by binding with fluoride anion. In the absence of anions, 2 is characterized by deep green colour. Upon gradual addition of F\(^-\), the colour becomes yellowish. This colour change exclusively occurs with F\(^-\) and no detectable change in colour is observed with other halogen anions such as Cl\(^-\), Br\(^-\) and I\(^-\). This anion-induced red-shift show naked-eye detectable color change. Titration of 2 with fluoride anion gave 1/2 binding isotherm and the Jop-plot shown in Figure 2 confirms the binding ratio. The calculated association constants for fluoride were \(K_1 = 3.0 \times 10^4 \text{ M}^{-1}\) and \(K_2 = 1.2 \times 10^5 \text{ M}^{-1}\)

The binding stoichiometry of 2 with fluoride anion may indicate that one host molecule bind with two fluoride anions. Similar titration behaviour was observed with compound 3 with fluoride anion. The obtained binding constant was almost identical within the experimental error with those of compound 2. These observations indicate that the existence of additional hydrogen-bonding donor do not enhance the binding constant as predicted. Degree of distortion of the molecule from planarity in 3 must be somewhat larger than that of 2. Thus the pyrrolic NH in the core may not be available for hydrogen bonding.

In summary, several meso-substituted phlorins was synthesized and anion-binding properties were studied. The results indicate that phlorins could be excellent host for fluoride anion. It is also possible to conceive the use of phlorin in colorimetric sensing systems due to the dramatic color changes by forming host-guest complexes. Synthesis of various analogues and their anion binding activities are under investigation.

Experimental Section

\(^1\)H NMR spectra (400 MHz, Bruker DPX-400) were recorded in CDCl\(_3\) with TMS as the internal standard. FAB mass spectra were obtained on AUTO SPEC M-363 high-resolution mass spectrometer. UV-Vis spectra were recorded on Cary-100 spectrometer. Column chromatography was performed on silica (Merck, 230–400 mesh). Pyrrole was distilled at atmospheric pressure from CdCl\(_2\). All other reagents were obtained from Aldrich and used as received unless noted otherwise.

5,5,15,15-Tetramethyl-10,20-diphenylporphodimethene (9), 5-oxo-10,15,20-tri-phenylphlorin (10) and 5,10,15,20-tetraphenylporphorin (11). Compound 6 (302 mg, 1.7 mmol), 8 (386 mg, 1.7 mmol), NH\(_2\)Cl (937 mg, 17.5 mmol) and benzaldehyde (352 \(\mu\)L, 3.46 mmol) were dissolved in acetonitrile (174 mL). The mixture was stirred for 5 min then added BF\(_3\)OEt \(_2\) (44 \(\mu\)L, 0.347 mmol). The whole mixture was stirred for 30 min at room temperature then added triethylamine (2 mL) in order to quench the reaction. The mixture was combined with DDQ (0.18 g, 5.20 mmol) and stirred for 1 h at room temperature. The whole mixture was extracted with methylene chloride (20 mL \(\times\) 3) after adding 30 mL of water. The organic layer was dried (Na\(_2\)SO\(_4\)) and the solvent was removed \(\text{in vacuo}\). The resulting black solid was separated by column chromatography on silica (CH\(_2\)Cl\(_2\)) to remove 5-oxophlorin 10. The second fraction containing 9 and 11 were separated by additional column chromatography on silica (CH\(_2\)Cl\(_2\)/Hexanes = 1/2). Each compound was recrystallized from methanol to afford analytically pure products. Yield for (9) 40 mg (9%); \(^1\)H NMR (CDCl\(_3\)) \(\delta 1.95\) (s, 12H, CH\(_3\)) 6.24 (d, \(J = 4.2\) Hz, 2H, 2H, 2H, 2H, 2H).
pyrrole-H). 6.33 (d, J = 4.2 Hz, 2H, pyrrole-H), 7.38-7.45 (m, 10H, Ar-H). 14.2 (br s 2H, NH); FAB-MS Caled. for C₉H₂N₂O, 200.26. Found 201.22, (M+'). Yield for (11) 19 mg (4%). 1H NMR (CDCl₃) δ = 2.78 (s, 12H, NH). 7.73-7.78 (m, 12H, Ar-H), 8.21-8.23 (m, 8H, Ar-H), 8.84 (s, 8H, pyrrole-H). For (10) Yield 6 mg (1%). 1H NMR (CDCl₃) δ = 1.68 (s, 2H, NH), 7.71-7.79 (m, 10H, Ar-H), 8.13-8.16 (m, 5H, Ar-H), 8.64 (d, J = 8.6 Hz, 2H, pyrrole-H), 8.71 (d, J = 8.6 Hz, 2H, pyrrole-H), 8.94 (d, J = 8.8 Hz, 2H, pyrrole-H), 9.12 (d, J = 8.8 Hz, 2H, pyrrole-H). FAB-MS Caled for C₉H₂N₂O (554.21). Found (556.39) (M+2).

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References


6. A typical procedure for the synthesis of 6. To a stirred mixture of pyrrole (6.9 mL, 86.1 mmol) and acetone (1.3 mL, 72.1 mmol) was added trifluoroacetic acid (0.13 mL, 1.72 mmol). The mixture was stirred for 5 min at room temperature and the mixture was combined with aqueous NaOH (0.1 N, 50 mL). The mixture was extracted with methylene chloride and solvent was removed in vacuo. Vacuum distillation using Kugelrohr (120 °C, 0.05 mmHg) gave pure product as white solid. Yield 1.8 g (69%)

1H NMR (CDCl₃) δ 1.63 (s, 6H, methyl), 6.08 (m, 2H, pyrrolic-H), 6.13 (m, 2H, pyrrole-H), 6.41 (m, 2H, pyrrole-H), 7.70 (brs, 2H, NH).
