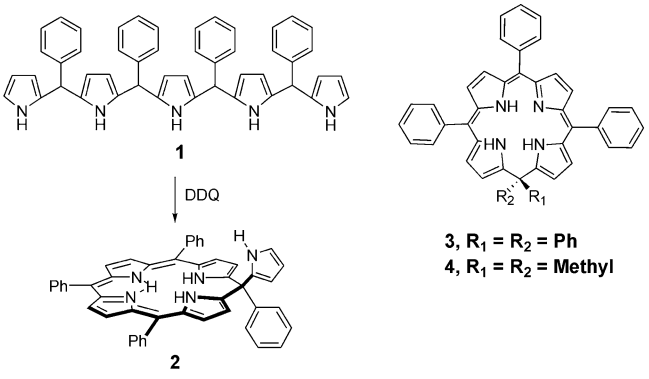
Novel Synthesis of Phlorin Derivatives and Their Anion Binding Properties

Seong-Jin Hong, Jae-Won Ka, Dong-Hoon Won, and Chang-Hee Lee*

Institute of Basic Science and Department of Chemistry, Kangwon National University, Chun-Chon 200-701, Korea
Received February 4, 2003

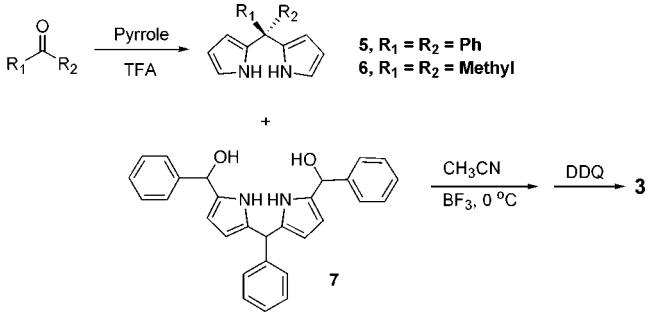
Key Words : Phlorins, Oxophlorin, Calix[4]phyrin, Chromogenic sensor

Phlorins are one of the intermediate structures between calix[4]pyrrole and porphyrin. Phlorins bearing one sp^3 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, bridging 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 **1** which was easily converted to the corresponding porphyrin under strongly acidic conditions.[3]



The fully *meso*-oxidized macrocycles, porphyrins are cation coordinating while the reduced porphyrin analogues has 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.

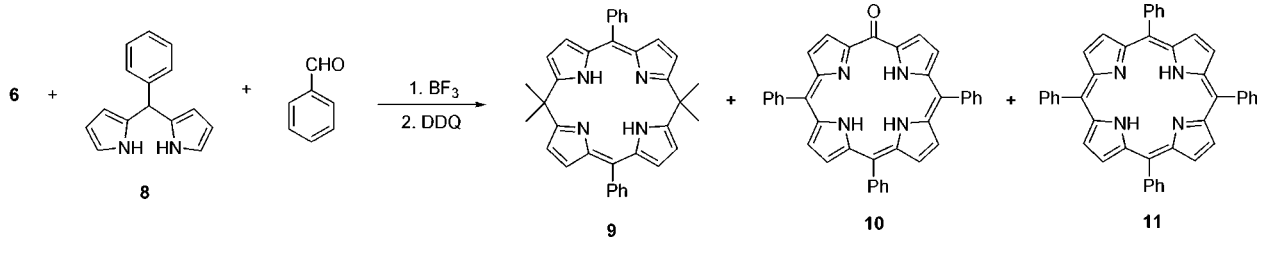
Sessler *et al*. reported an attempted synthesis of compound **4** by acid catalyzed condensation of tetrapyrrotrimethane (linear tetrapyrrolic oligomer) with acetone, resulting unexpected isolation of *meso*-hydroxylated calixphyrin.[5] Our approaches for the synthesis of compound **3** and 4 are shown 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]



Scheme 1

The condensation of acetone with pyrrole afforded *meso*-dimethyldipyrromethane **6** in 60% yield while condensation of the benzophenone with pyrrole gave lower (12%) yield of **5**. Then diol **7** synthesized as previously reported procedure[7] was used as southern half of the expected product. Treatment of **7** with **5** in acetonitrile in the presence of BF_3, 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*-dimethyldipyrromethane **6**, benzaldehyde and *meso*-phenyldipyrromethane **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.*



Scheme 2

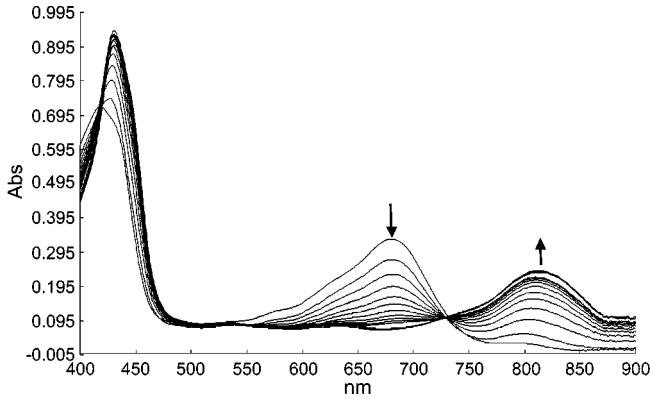


Figure 1. UV-Vis. Spectral titration with tetrabutylammonium fluoride (TBAF). [**2**] = 2.65×10^{-5} M in $CHCl_3$ at 25 °C. Each spectrum was taken after adding 0.1 equiv. of guest.

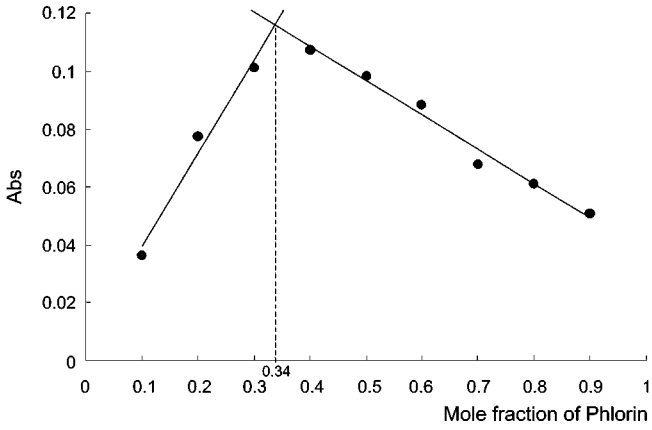


Figure 2. Job plot for **2** with TBAF, [**2**] = 4.2×10^{-5} M in $CHCl_3$ at 25 °C.

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 weres $K_1 = 3.0 \times 10^4$ M^{-1} and $K_2 = 1.2 \times 10^5$ 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

^1H 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 CaH_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-tetraphenylporphyrin (11). Compound **6** (302 mg, 1.7 mmol), **8** (386 mg, 1.7 mmol), NH_4Cl (937 mg, 17.5 mmol) and benzaldehyde (352 μL, 3.46 mmol) were dissolved in acetonitrile (174 mL). The mixture was stirred for 5 min then added $BF_3 \cdot OEt_2$ (44 μL, 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 × 3) after adding 30 mL of water. The organic layer was dired (Na_2SO_4) and the solvent was removed *in vacuo*. The resulting black solid was separated by column chromatography on silica (CH_2Cl_2) to remove 5-oxophlorin **10**. The second fraction containing **9** and **11** were separated by additional column chromatography on silica (CH_2Cl_2/Hexanes = 1/2). Each compound was recrystallized from methanol to afford analytically pure products. Yield for (**9**) 40 mg (9%); ^1H NMR ($CDCl_3$) δ 1.95 (s, 12H, CH_3), 6.24 (d, J = 4.2 Hz, 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 Calcd. for $C_{36}H_{32}N_4$ 520.26, Found 521.22 (MH^+). Yield for (**11**) 19 mg, (4%); ^{1}H NMR ($CDCl_3$) 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%); ^{1}H NMR ($CDCl_3$) 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 Calcd for $C_{38}H_{26}N_4O$ (554.21), Found (556.39) (M^++2).

Acknowledgments. This work was supported by grants from the Korea Science and Engineering Foundation (KOSEF R05-2000-000-00077-0). The NMR and mass data were obtained from the central instrumental facility in Kangwon National University.

References

1. (a) Setsune, J.; Yamaji, H.; Kaito, T. *Tetrahedron Lett.* **1990**, *31*, 5057-5060. b) Setsune, J.; Ikeda, M.; Iida, T.; Kitao, T. *J. Am. Chem. Soc.* **1988**, *110*, 6572-6574. (b) Khoury, R. G.; Jaquinod, L.; Shachter, A. M.; Nelson, N. Y.; Smith, K. M. *Chem. Commun.* **1997**, 215.
2. (a) Ruppert, R.; Jeandon, C.; Sgambati, A.; Callot, H. J. *Chem. Commun. (Cambridge)* **1999**, 2123-2124. b) Krattinger, B.; Callot, H. J. *Tetrahedron Lett.* **1996**, *37*, 7699-7702.
3. (a) Ka, J. W.; Lee, C. H. *Tetrahedron Lett.* **2000**, *41*, 4609-4612. (b) Dolphin, D. *J. Heterocyclic Chem*. **1970**, *7*, 275-283.
4. (a) Sessler, J. L.; Anzenbacher Jr., P.; Jursikova, K.; Miyaji, H.; Genge, J. W.; Tvermoes, N. A.; Allen, W. E.; Shriver, J. A. *Pure & Appl. Chem*. **1998**, *70*, 2401-2408. (b) Sessler, J. L.; Zimmerman, R. S.; Bucher, C.; Kral, V.; Andrioletti, B. *Pure & Appl. Chem*. **2001**, *73*, 1041-1057.
5. Bucher, C.; Siedel, D.; Lynch, V.; Kral, V.; Sessler, J. L. *Org. Let.* **2000**, *2*, 3103-3106.
6. A typical procedure for the synthesis of **6**: To a stirred mixture of pyrrole (6.0 mL, 86.1 mmol) and acetone (1.3 mL, 7.21 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 and pyrrole was removed *in vacuo*. Vacuum distillation using Kugelrohr (120 ^{o}C, 0.05 mmHg) gave pure product as white sold. Yield 1.8 g (60%): ^{1}H NMR ($CDCl_3$) δ 1.63 (s, 6H, methyl), 6.08 (m, 2H, pyrrolic-H), 6.13 (m, 2H, pyrrolic-H), 6.61 (m, 2H, pyrrolic-H), 7.70 (brs, 2H, NH).
7. (a) Lee, C. H.; Li, F.; Iwamoto, K.; Dadok, J.; Bothernerby, A.; Lindsey, J. S. *Tetrahedron* **1995**, *51*, 11645-11672. (b) Cho, W. S.; Kim, H. J.; Littler, B. J.; Miller, M. A.; Lee, C. H.; Lindsey, J. S. *J. Org. Chem.* **1999**, *64*, 7890-7901.
8. Clezy, P. S.; Liepa, A. J. *Aust. J. Chem*. **1970**, *23*, 2461-2476.