

Synthesis of functionalized thia analogues of phlorins and covalently linked phlorin–porphyrin dyads†

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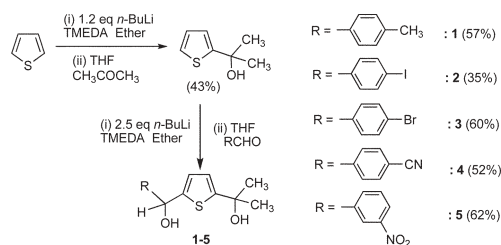
The 21,23-dithia and 21-thia analogues of phlorins and mono-functionalized thiaphlorins were synthesized using easily available precursors and the mono-functionalized thiaphlorins were used further to synthesize the first examples of three covalently linked thiaphlorin–porphyrin dyads.

Calix[4]pyrins are a class of hybrid molecules that lie at the structural crossroads between porphyrins¹ and calix(4)pyrroles² and contain four pyrroles bridged *via* a mixture of sp²- and sp³-hybridized *meso* carbon atoms.³ Phlorins are a class of calix[4]pyrins {calix(4)pyrin-(1.1.1.1.)} containing three sp² and one sp³ *meso* carbon atoms and were first identified by R. B. Woodward during his landmark studies towards the synthesis of chlorophyll *a*.⁴ Phlorins are also proposed to be intermediates in the catalytic cycle of the haem p460 of hydroxylamine oxidoreductase⁵ and some syntheses of porphyrins⁶ and chlorins.⁷ Phlorins are found to be good anion sensors and were obtained on reduction of porphyrins and metalloporphyrins by photochemical,⁸ radiolytic,⁹ electrochemical¹⁰ and chemical¹¹ methods. However, phlorins are in general too poorly stable to explore their complete potential for various applications. Recently, several methods have become available to obtain stable phlorins in metalated and metal free forms. In particular, Setsune *et al.*,¹² Callot *et al.*¹³ and Lee *et al.*¹⁴ developed independently some novel routes to synthesize phlorins starting from porphyrins or oligopyrroles as precursors. A perusal of the literature reveals that, to the best of our knowledge, there have been no reports on hetero analogues of phlorins to test their potential as receptors for cations as well as for anions. Our group has been involved in the design and synthesis of functionalized heteroporphyrins and their use in the synthesis of covalent and non-covalent unsymmetrical porphyrins.¹⁵ In this paper, we report the synthesis of functionalized thiaphlorins and their use in the synthesis of thiaphlorin–porphyrin dyads.

1 was synthesized by treating the thiophene mono-ol, 2- $\{(\alpha,\alpha'$ -dimethyl)hydroxymethyl\}thiophene with 2.5 equivalents of *n*-BuLi which was followed by 1.2 equivalents of *p*-tolylaldehyde in THF at 0 °C. The crude compound was purified by column chromatography on silica and afforded the pure unsymmetrical

thiophene diol **1** in 57% yield. The functionalized unsymmetrical thiophene diols **2–5** were synthesized similarly in 35–62% yields by treating the lithiated mono-ol, 2- $\{(\alpha,\alpha'$ -dimethyl)hydroxymethyl\}thiophene with functionalized aromatic aldehydes such as *p*-iodobenzaldehyde, *p*-cyanobenzaldehyde, *p*-bromobenzaldehyde and *m*-nitrobenzaldehyde in THF at 0 °C followed by column chromatographic purification (Scheme 1). The diols **1–5** were characterized by mp, infra-red, NMR, mass and elemental analysis. The other desired precursor, the symmetrical 16-thiatripyrrane **6**, was synthesized by following the literature.¹⁵

The 21,23-dithiaphlorins **7–11** were prepared as shown in Scheme 2. Condensation of one equivalent of unsymmetrical thiophene diols **1–5** with one equivalent of 16-thiatripyrrane **6**¹⁶ in dichloromethane, in the presence of catalytic amount of trifluoroacetic acid at room temperature and under a nitrogen atmosphere, followed by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) afforded 21,23-dithiaphlorins **7–11**. After standard work-up, the resulting crude compound was subjected twice to silica gel column chromatography and dithiaphlorins **7–11** were obtained in 7–19% yields. The 21-monothiaphlorins **12–16** were synthesized in 3–9% yields by condensing one equivalent of the diols **1–5** with two equivalents of *p*-tolylaldehyde and three equivalents of pyrrole under the same acid catalysed conditions (Scheme 2) followed by silica gel column chromatographic purification. The thiaphlorins **7–16** are quite stable and were characterized by NMR, mass, elemental analysis and absorption spectroscopy. The presence of strong M⁺ ion peak in the mass spectra and matching elemental analysis confirmed the thiaphlorins **7–16**. In ¹H NMR of **7–11**, the four β -pyrrole protons appeared as four sets of signals, either doublets or broad singlets and are significantly upfield shifted to the 6.3–7.1 ppm region as compared to the 21,23-dithiaporphyrins due to the diminished aromatic π -conjugation. The four β -thiophene protons appeared as two sets of signals; a doublet at ~7.2 ppm was due to one proton and a multiplet at ~7.3 ppm was due to three protons. The inner NH proton appeared as two broad signals at ~11.3 and ~12.7 ppm which was attributed tentatively to the presence of

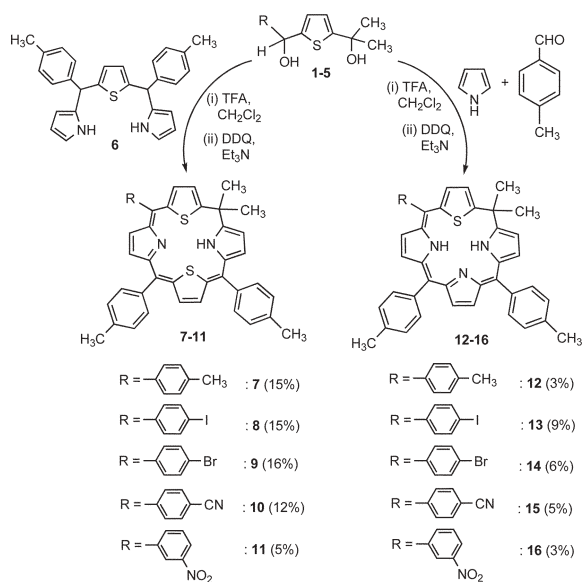


Scheme 1 Synthesis of unsymmetrical thiophene diols **1–5**.

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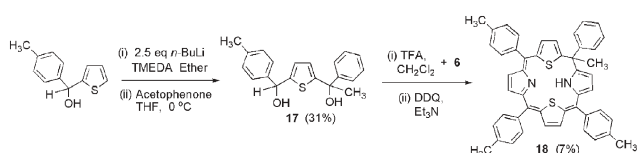
† Electronic supplementary information (ESI) available: Experimental, NMR, mass, absorption and emission spectral data of selected compounds; anion binding studies of compounds **7**, **19** and **20**. See DOI: 10.1039/b607013b



Scheme 2 Synthetic routes for mono-functionalized 21,23-dithia and 21-thiaphlorins.

tautomers in solution. In ^1H NMR of **12–16**, the six β -pyrrole protons appeared mainly as three sets of signals; two multiplets and one broad singlet and were upfield shifted to 6.5–6.9 ppm region as compared to 21-thiaporphyrin. The two β -thiophene protons appeared as one broad singlet at ~ 7.2 ppm. The two inner NH protons appeared as three sets of broad singlets at 9.9, 11.8 and 12.0 ppm which may be because of the presence of tautomers in solution. Though we tentatively assigned the number of NH signals observed to be due to the presence of tautomers, detailed NMR studies will be carried out in future to resolve this ambiguity and reported in due course. The absorption spectra of **7–11** showed broad Q-type bands at ~ 695 nm and broad and sometimes split moderately intense Soret type absorptions at ~ 420 nm.

Unfortunately we did not get suitable crystals of **7–16** for structure determination. Thus, we prepared phlorin **18** as shown in Scheme 3. The desired diol **17** was prepared by treating 2-(*p*-tolylhydroxymethyl)thiophene with 2.5 equivalents of *n*-BuLi followed by acetophenone under standard conditions. The diol **17** was condensed with **6** under mild acid conditions and afforded pure **18** in 7% yield. Single crystals of **18** could be obtained by slow evaporation of **18** in CH_2Cl_2 . \ddagger The structure could be solved which is slightly disordered and is shown in Fig.1. \dagger As seen from Fig. 1, the structure is not planar and possesses a marked kink at the alkyl substituted sp^3 hybridized *meso* carbon. The inner NH atom is present on the pyrrole N which is adjacent to *meso* sp^3 carbon. To accommodate the deformation and steric hindrance caused by the *meso* sp^3 carbon atom, the pyrrole and the thiophene rings adopted an alternate conformation.



Scheme 3 Synthesis of dithiaphlorin **18**.

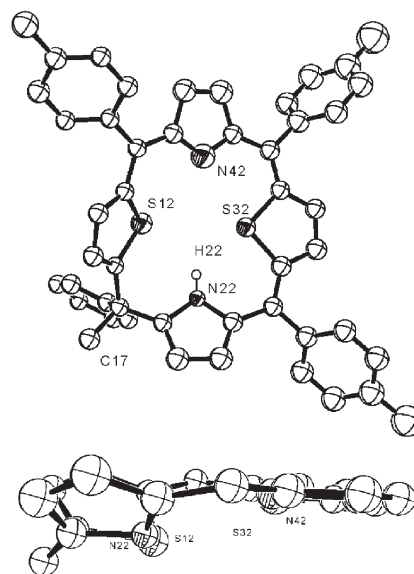


Fig. 1 X-Ray structures of dithiaphlorin **18**. Thermal ellipsoids are shown at the 50% probability level. At the bottom view *meso* aryl groups are removed for clarity.

The use of mono-functionalized thiaphlorins was demonstrated by synthesizing the first examples of three covalently linked diarylethene bridged dyads **19–21** containing thiaphlorin and porphyrin sub-units (Chart 1). This kind of dyads may have several potential applications including as optical sensors. The dyad **19** containing 21,23-dithiaphlorin and ZnN_4 porphyrin sub-units was synthesized by coupling of **8** with zinc(II)5,10,15-tri(mesityl)-20-(*p*-ethynylphenyl)porphyrin **22** 17 in toluene–triethylamine at 50°C in the presence of catalytic amounts of AsPh_3 – $\text{Pd}_2(\text{dba})_3$ under the conditions developed by Lindsey and co-workers 18 for Sonogashira coupling (Scheme 4).

The crude compound was purified by column chromatography on neutral alumina using petroleum ether–3–5% ethyl acetate and afforded dyad **19** in 35% yield. Similarly, dyad **20** containing 21,23-dithiaphlorin and 21-thiaporphyrin (N_3S) sub-units was synthesized in 48% yield by coupling of **8** with 5-(*p*-ethynylphenyl)-10,15,20-tris-(*p*-octyloxyphenyl)-21-monothia-porphyrin 15 under

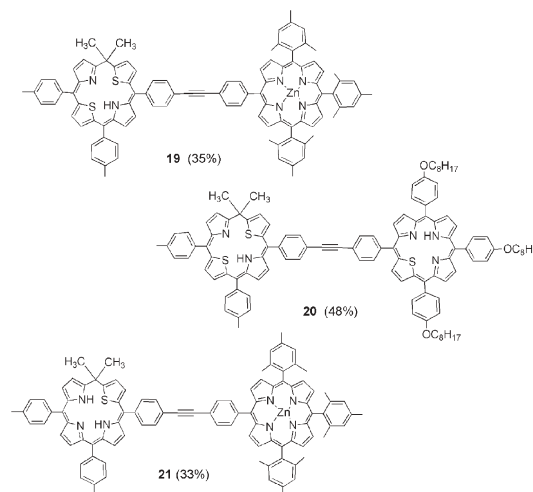
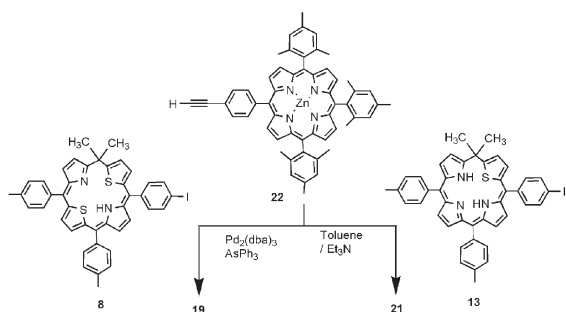


Chart 1 Structures of porphyrin–thiaphlorin dyads **19–21**.



Scheme 4 Synthesis of porphyrin–thiaphlorin dyads **19** and **21**.

similar reaction conditions. The dyad **21** containing 21-monothiaphlorin and ZnN₄ porphyrin subunits was also synthesized in a similar way by the coupling of **13** and **22** (Scheme 4).¹⁸ The dyads **19–21** are highly soluble in common organic solvents and characterized by NMR, mass and absorption spectroscopic techniques. The ES-MS mass spectra showed an M⁺ ion peak confirming the dyads **19–21**. The ¹H NMR spectra of **19–21** showed peaks corresponding to both the monomeric thiaphlorin and porphyrin sub-units in dyads **19–21** that interact very weakly. The absorption spectra of **19–21** are essentially a linear combination of the spectra of the corresponding monomers with only minor differences in wavelength maxima and band shapes, indicating that the monomeric sub-units retain their individual identities in the dyads **19–21**.

The preliminary binding studies for halides as well as other anions like HSO₄⁻ and SCN⁻ have been carried out¹⁹ with protonated forms of the monomeric 21,23-dithiaphlorin **7** and dyads **19** and **20**. The protonated species of **7** was generated by careful addition of a dilute solution of trifluoroacetic acid (2 × 10⁻² M) to **7** (1.5 × 10⁻⁶ M) in dichloromethane. On addition of trifluoroacetic acid to **7**, the colour of the solution changes from green to light yellow. While a detailed study is needed, the preliminary investigation indicated that the protonated form of **7** binds halide anions as well as other anions as judged from optical studies.¹⁹† The protonated form of **7** showed a strong peak at 825 nm which decreased its intensity when it was titrated with increasing amounts of anionic salts, confirming the binding of an anion. The binding constants were evaluated using a 1 : 1 binding model.²⁰†

The binding studies were also carried out with dyad **19**, which has the Zn(II) ion in the porphyrin sub-unit, by selectively protonating the 21,23-dithiaphlorin sub-unit with dilute trifluoroacetic acid without inducing the demetalation of the porphyrin sub-unit.† For the protonated form of dyad **19**, when titrated with tetrabutylammonium iodide salt, the decrease in the intensity of the absorption band at 842 nm supported the binding of anion at the 21,23-dithiaphlorin sub-unit site.† Thus, the dyad **19** is the novel system which binds anion and cation simultaneously. We also tested the dyad **20** which contains free base 21-thiaphlorin and 21,23-dithiaphlorin sub-units as a fluorescent sensor. Since the 21,23-dithiaphlorin sub-unit is more basic than the 21-thiaphlorin sub-unit in dyad **20**, it is possible to selectively protonate the 21,23-dithiaphlorin sub-unit and the binding of anions at the protonated 21,23-dithiaphlorin site could be then sensed by observing the changes in the fluorescence band of the 21-thiaphlorin sub-unit. It is observed that the addition of

the increasing amounts of tetrabutylammonium iodide salt to the protonated form of dyad **20** resulted in the gradual enhancement of intensity of the 21-thiaphlorin fluorescent band. This suggests that the iodide ion was bound at the protonated 21,23-dithiaphlorin site in dyad **20**, which was reflected in the changes in the intensity of the fluorescent band of the 21-thiaphlorin sub-unit, thus acting like a fluorescent sensor.† More studies are underway and will be reported in due course.

In conclusion, we report the first synthesis of 21,23-dithiaphlorins and 21-monothiaphlorins containing one sp³ meso carbon using easily available precursors. The method is simple, facile, and allows the synthesis of any desired mono-functionalized thia analogues of phlorin. The mono-functionalized thiaphlorins were used further to synthesize the first examples of covalently linked thiaphlorin–porphyrin dyads. The anion binding studies indicated that the thiaphlorin and thiaphlorin–porphyrin dyads exhibit very interesting anion binding properties.

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Notes and references

‡ Crystal data for C₄₈H₃₈N₂S₂. *M* = 706.92, monoclinic, space group *P2₁/n* (No. 14), *a* = 8.990(1), *b* = 16.034(1), *c* = 25.816(1) Å, β = 98.78(1)°, *V* = 3677.7(5) Å³, *D_c* = 1.277 g cm⁻³, μ = 1.83 cm⁻¹, *Z* = 2, λ = 0.71073 Å, *T* = 198 K, 19039 reflections collected (±*h*, ±*k*, ±*l*), [(sinθ)/λ] = 0.59 Å⁻¹, 6457 independent (*R_{int}* = 0.050) and 4623 observed reflections [*I* ≥ 2σ(*I*)], 492 refined parameters, *R* = 0.064, w*R*² = 0.169. CCDC 235993. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b607013b

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