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First synthesis of a series of core-modified tetrabenzoporphyrins

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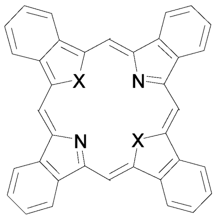
Successful synthesis of a series of highly conjugated porphyrin analogues, including thia-, dithia- and oxathia-tetrabenzoporphyrins, and their optical properties are reported.

Tetrabenzoporphyrin (TBP) and its related metal complexes are well-known conjugated porphyrins with intriguing optical properties in near infra red and have been intensively studied owing to their potential applications as opto-electronic materials, near-IR dyes or nonlinear optical materials.[1] The design of their electronic structures by chemical modification is interesting from a fundamental point of view and provides a challenging theme for synthetic chemists. Several synthetic problems have arisen in this area of research, *e.g.* the instability of isoindole and the low solubility of TBP derivatives.[2] We are currently interested in the core modification of porphyrin systems by substitution of pyrrole nitrogens with other heteroatoms such as sulfur or oxygen because it is a powerful method for modifying the various properties of such compounds.[3] In addition, water-soluble core-modified porphyrins have recently emerged as a potentially useful agent in photodynamic therapy (PDT) applications due to their ability to absorb long-wavelength radiation.[4] Here, we report the synthesis and spectroscopic properties of thia-, dithia- and oxathia-TBPs **1** as the first examples of core-modified TBPs.



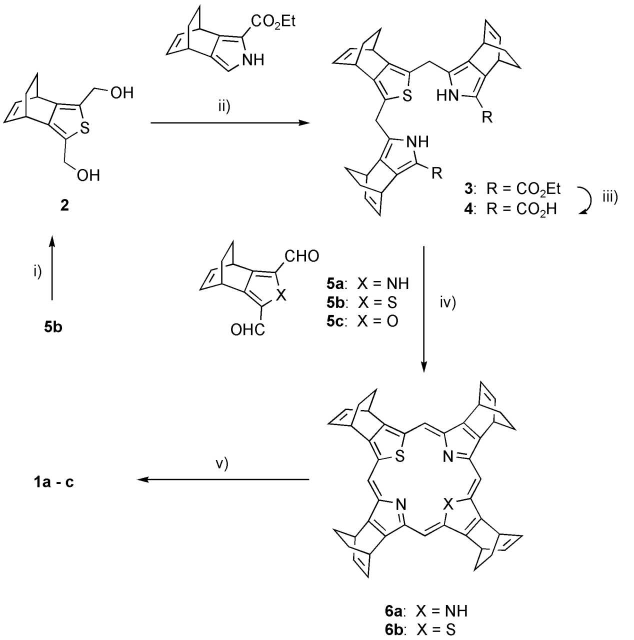
X = NH, NH **TBP**
X = S, NH **1a**
X = S, S **1b**
X = S, O **1c**

If we were to apply common porphyrin synthesis methods to the preparation of **1**, highly reactive *o*-quinonoid heterocycles such as isoindole, isothianaphthene[5] and isobenzofuran[6] would be required. However, these are too labile to use as starting materials for the construction of **1**. Thus, we applied the retro Diels–Alder strategy developed by our group in the synthesis of TBP derivatives by using bicyclo[2.2.2]octadiene (BCOD)-fused heterocycles as synthons of the *o*-quinonoid heterocycles.[2]

The synthesis of BCOD-fused porphyrins **6** and their conversion to the corresponding core-modified TBPs **1** are outlined in Scheme 1. We adopted the [3+1] approach[1] and the tripyrrane analogue with a central thiophene ring **3** was prepared by the acid-catalyzed condensation of α,α′-bis(hydroxymethyl)thiophene **2** with ethyl 4,7-dihydro-4,7-ethano-2*H*-isoindole-1-carboxylate.[7] Hydrolysis of the ester groups with lithium hydroxide afforded dicarboxylic acid **4** in 98% yield. The requisite BCOD-fused pyrrole,[2] thiophene,[8] furan[9] and their derivatives including dialdehydes **5** were prepared according to the reported procedures.[10] Condensation of **4** with **5a–c** in the presence of TFA in CH_2Cl_2 followed by oxidation with DDQ gave the desired macrocycles **6a–c** as mixtures of diastereomers in 42, 37 and 23% yields, respectively.

Compounds **6** were fully characterized by ^1H NMR spectroscopy, mass spectrometry and elemental analyses.† The ^1H NMR spectra of **6** in $CDCl_3$ showed characteristic multiple signals between 10.0 and 11.0 ppm due to *meso*-protons. In monothiaporphyrin **6a**, the shielded internal NH proton was observed at −4.6 ppm. The FAB mass spectra of **6** exhibited the strong ion peaks ($M^+ - 4C_2H_4$) owing to the loss of four ethylene moieties, and thermogravimetric analyses confirmed that the retro Diels–Alder reactions slowly occurred between 130 and 230 °C. Heating **6** at 230 °C under a vacuum (2 mmHg) for 30 min gave the corresponding core-modified TBPs **1** as dark green solids in essentially quantitative yields. The solubilities of **1** were slightly increased relative to parent TBP, which implied a distorted structure due to the interaction of sulfur in the core.[11] The elemental analyses of these products were satisfactory without purification.

The UV-vis spectra of **6b**, **1b** and the dication of **1b** are shown in Fig. 1 as typical examples. The absorption spectrum of **6b** was similar to that of *meso*-unsubstituted dithiaporphyrin reported by Broadhurst *et al.*, although the prominent reduction of the intensity of the Soret band was not observed in this case.[12]† The split Soret and strong Q bands evident in the spectrum of **1b** were also observed in the spectrum of TBP. Comparison of the spectra of **6b** and **1b** revealed a significant bathochromic shift of all the absorption bands due to expansion of the π-system. Addition of trace amounts of TFA to **1b** provided a dication species whose spectrum showed broad Soret and four Q band absorptions at 445, 474(sh), 633, 661, 687 and 728 nm, respectively. The absorption and emission data of TBP and core-modified TBPs **1** are summarized in Table 1. Proportional bathochromic shifts were observed in the porphyrin electronic absorption and emission bands as the number of the sulfur atoms increased. The very low



Scheme 1 *Reagents, conditions and yields*: i) $NaBH_4$, CH_2Cl_2, MeOH, 0 °C, 30 min, 78%; ii) TFA, $CHCl_3$, 50 °C, 5h, 90%; iii) LiOH, THF, EtOH, H_2O, reflux, 16 h, 98%; iv) TFA, CH_2Cl_2, rt, 16 h, then Et_3N, DDQ, 23–42%; v) 230 °C, 30 min, *in vacuo* (2 mmHg), quant.

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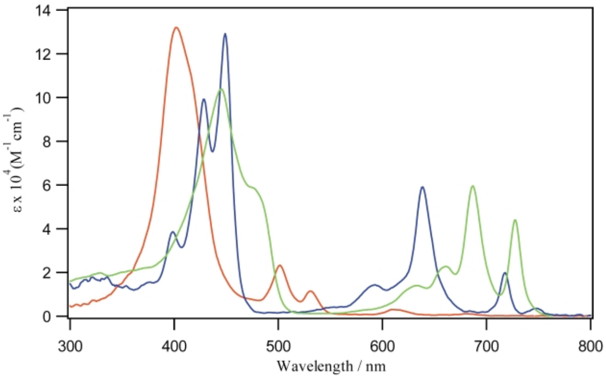

Fig. 1 UV-vis spectra of **6b** in CH_2Cl_2 (red line), **1b** in DMF (blue line) and dication **1b** in 1% TFA–CH_2Cl_2 (green line).

Table 1 Absorption and emission data of TBP and **1a–c** in DMF

Compd.	λ_{abs}/nm ($\log_{10} \varepsilon$)	λ_{em}/nm^a	$\Phi_f^{a,b}$
TBP^c	385(4.11), 412(4.87), 427(4.93), 565(3.49), 596(4.34), 604(4.26), 611(4.07), 662(4.20)	658	0.46
1a	394(4.41), 423(4.89), 442(5.01), 584(3.94), 620(4.51), 629(4.44), 639(4.29), 692(4.21)	693	0.053
1b	399(4.59), 429(4.99), 449(5.11), 593(4.15), 639(4.77), 718(4.30)	718	0.013
1c	394(4.62), 421(4.87), 444(5.09), 592(4.21), 637(4.80), 714(4.16)	714	0.018

^{a} Measured by excitation of the Soret band. ^{b} Fluorescence quantum yields were calculated against TPP in benzene (ref. 13). ^{c} Ref. 14.

fluorescence quantum yields of **1** may be attributed to the internal heavy atom effect of sulfur and distortion of the chromophores.[15] The absorption spectra of the TBP analogues with two heteroatoms, **1b** and **1c**, were quite different from that of TBP.[14b] In TBP, three split Q bands were observed around 600 nm, while the spectra of **1b** and **1c** showed one 2.8 times stronger absorption around the same region (Table 1). As expected, the substitution of nitrogen atoms by sulfur in the TBP core also induced a strong bathochromic shift of the Q bands. It should be noted that the longest-wavelength absorption maximum of **1b** at 718 nm (ε = 1.99 × 10^4 M^{-1} cm^{-1}) is more bathochromically shifted and 4.3 times stronger than that of the well-studied tetraphenyl-21,23-dithiaporphyrin (λ_{max} = 699 nm, ε = 4.63 × 10^3 M^{-1} cm^{-1}).[16]

In summary, we have synthesized a new series of core-modified TBPs **1**, which show considerable bathochromic shifts in both absorption and emission spectra. These spectroscopic features indicate that TBPs **1** have potential as photosensitizers in PDT. In addition, this synthetic strategy can be utilized for the construction of other core-modified porphyrinoid systems. Further studies on the synthesis and characterization of novel highly conjugated macrocycles are underway in our laboratory.

Notes and references

† *Selected spectroscopic data*: **6a**: (a mixture of diastereomers) green–brown solid, mp > 130 °C (decomp.); δ(400 MHz, $CDCl_3$) −4.61 (s, 1H), 1.82–2.01 (m, 8H), 2.13 (m, 4H), 2.28 (m, 4H), 5.57 (m, 4H), 5.87 (m, 2H), 6.04 (m, 2H), 7.06 (m, 4H), 7.21–7.25 (m, 4H) 10.39 (m, *meso*-H, 2H), 10.90 (m, *meso*-H, 2H); *m/z* (FAB) (%) 640 (M^+ + H, 44), 612 (10), 584 (9), 556 (32), 528 (100); λ_{max} (CH_2Cl_2)/nm ($\log_{10} \varepsilon$) 394 (5.14), 497 (4.32), 528 (4.08), 590 (3.67), 663 (3.31). The analytical sample of **6a** was obtained by recrystallization from CH_2Cl_2–MeOH, and contained *ca.* a quarter molar ratio of CH_2Cl_2, as determined by ^1H NMR analysis. Calcd. for $C_{44}H_{37}N_3S\cdot\frac{1}{4}CH_2Cl_2$: C, 80.39; H, 5.72; N, 6.36. Found: C, 80.30; H, 6.00; N, 6.17%. **6b**: (a mixture of diastereomers) green–brown solid, mp > 130 °C (decomp.); δ (400 MHz, $CDCl_3$) 1.83–2.02 (m, 8H), 2.13 (m, 4H), 2.29 (m, 4H), 5.55 (m, 4H), 6.04 (m, 4H), 7.03–7.06 (m, 4H), 7.26 (m, 4H), 10.94 (m, *meso*-H, 4H); *m/z* (FAB) (%) 657 (M^+ + H, 35), 629 (11), 601 (9), 573 (29), 545 (100); (CH_2Cl_2) λ_{max} (CH_2Cl_2)/nm ($\log_{10} \varepsilon$) 402 (5.12), 502 (4.36), 531 (4.06), 611 (3.47), 680 (3.04). The analytical sample of **6b** was obtained by recrystallization from CH_2Cl_2–MeOH, and contained *ca.* a quarter molar ratio of CH_2Cl_2, as determined by ^1H NMR analysis. Calcd. for $C_{44}H_{36}N_2S_2\cdot\frac{1}{4}(CH_2Cl_2 + H_2O)$: C, 77.86; H, 5.46; N, 4.10. Found: C, 77.64; H, 5.80; N, 4.01%. **6c**: (a mixture of diastereomers) green–brown solid, mp > 130 °C (decomp.); δ (400 MHz, $CDCl_3$) 1.74–1.92 (m, 8H), 2.07 (m, 4H), 2.21–2.32 (m, 4H), 5.48 (m, 2H), 5.52, (m, 2H), 5.85 (m, 2H), 5.96 (m, 2H), 7.03–7.10 (m, 4H), 7.21–7.29 (m, 4H), 10.27 (m, *meso*-H, 2H), 10.80 (m, *meso*-H, 2H); *m/z* (FAB) (%) 641 (M^+ + H, 23), 613 (12), 585 (10), 557 (27), 529 (100); λ_{max} (CH_2Cl_2)/nm ($\log_{10} \varepsilon$) 396 (5.11), 496 (4.20), 529 (4.05), 613 (3.46), 677 (3.04). Anal. calcd. for $C_{44}H_{36}N_2OS\cdot\frac{1}{2}H_2O$: C, 81.32; H, 5.74; N, 4.31. Found: C, 81.34; H, 5.86; N, 4.15%. **1a**: dark green solid, mp > 300 °C. Anal. calcd. for $C_{36}H_{21}N_3S$: C, 81.95; H, 4.01; N, 7.96. Found: C, 81.87; H, 4.01; N, 7.81%. **1b**: dark green solid, mp > 300 °C. Anal. calcd. for $C_{36}H_{20}N_2S_2$: C, 79.38; H, 3.70; N, 5.14. Found: C, 79.68; H, 3.73; N, 5.00%. **1c**: dark green solid, mp > 300 °C. Anal. calcd. for $C_{36}H_{20}N_2OS$: C, 81.79; H, 3.81; N, 5.30. Found: C, 81.49; H, 4.02; N, 5.12%.

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