Reduction of *N*-arylporphyrins to *N*-arylphlorins: opposite stereochemical courses as a function of the reducing agent

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Electrochemical or $Na_2S_2O_4$ reduction of *N*-arylporphyrins gives stable phlorins epimeric to those obtained by tosylhydrazine or $NaBH_4$ reduction.

Phlorins are non-aromatic tetrapyrrolic macrocyclic isomers of chlorins. In these dihydroporphyrins the two additional hydrogens are located at the *meso* and N positions. The first stable phlorin was isolated by R. B. Woodward[1] during the synthesis of chlorophyll *a*. Factors favouring the formation of phlorins by chemical or electrochemical reduction or by nucleophilic addition to porphyrins are steric strain,[1,2] complexation with high valent metal ions,[3] and electrophilicity of the macrocycle.[4]

We found[5–7] that the reduction of *N*-arylporphyrins **1** with tosylhydrazine or $NaBH_4$ gave *N*-arylphlorins **2** (*N*,*meso*-dihydroporphyrins; *anti* isomer) instead of the expected *N*-arylchlorins (β,β-dihydroporphyrins). It was proposed that in this case the driving force of the reaction, as well as the explanation for the stability of the products, was the rotation experienced by the *N*-substituted pyrrole resulting in a significant decrease of the steric strain.

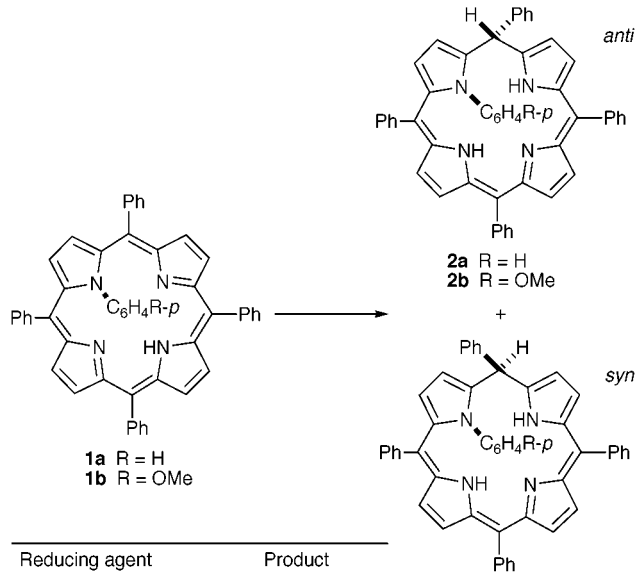
Recently,[8] a phlorin derived from heme *c* was proposed as an intermediate in the catalytic cycle of hydroxylamine oxidoreductase (HAO). This phlorin is a heme *c* group arylated at C-5 by a tyrosine moiety. The position of the aryl group above the plane in the intermediate strongly suggested an C-5 sp^3 carbon and thus a phlorin. Here we describe the preparation and structural characterization of new phlorins whose out-of-plane *meso*-aryl groups bear a resemblance to such intermediates.

We found that reduction of *N*-arylprophyrins **1** with aged $NaBH_4$ gave a mixture of the expected phlorin and a very similar product, at least where the UV-visible data were concerned. This product proved to be rather unstable under chromatographic conditions, but NMR data suggested an epimeric structure. In order to assign a structure to this new phlorin and to find conditions suitable for its preparation in acceptable yields, we tested a new set of reducing agents. Borane·THF was not satisfactory, giving mixtures of phlorins and dihydrophlorins *etc.*, but cathodic reduction, sodium dithionite and dihydropyridine **4** (Hantzsch ester) all gave quantitatively phlorins (Scheme 1).

Electrochemical reduction of *N*-aryl-*meso*-tetraphenylporphyrin **1** was performed in an electrolysis cell fitted with three compartments separated by glass frits (Hg cathode, Pt counter electrode, SCE reference electrode). The experiments were conducted on a 25 to 50 μmol scale in a protic electrolyte (THF–MeOH, 2:1; 0.25 M LiCl). The reduction of the porphyrin and the concomitant reduction of the protons led to an increase of the electrolyte basicity during electrolysis. Therefore, the working potential (−0.8 to −1.2 V *vs.* SCE) was continuously adjusted during the electrolysis in order to keep the current density approximatively constant (5 mA cm^{-2}). The progress of the reaction was followed by TLC and showed that only one reduction product was formed. A very simple work-up procedure (addition of CH_2Cl_2, washing with water and crystallisation of the crude product from CH_2Cl_2–MeOH) afforded the pure phlorins **3a** or **3b** as green crystals (60% isolated yield.) Phlorins **3a** and **3b** were found to be stable as solids and stable enough in solution to grow crystals (see below), but reverted to the starting *N*-arylporphyrins **1a** and **1b** rapidly when chromatographed.

Compounds **3a** and **3b** showed phlorin UV-visible spectra [**3a**: λ_{max} 422 nm (ε = 34000) and 685 (29700)]. The NMR spectra of **3a** and **3b** revealed the loss of aromaticity suffered by the porphyrin ring: the pyrrolic protons are located between *ca.* δ 6.5 and 7, the *meso* proton of **3b** was found at δ 6.87, a value 2.53 ppm downfield from that of the *meso* proton of **2b** (δ 4.34). Of particular interest are the signals of the *N*-anisyl group protons of **3b**: the aromatic protons appear at δ 5.78, 5.96, 6.13 and 6.29, strongly suggesting a face-to-face (*syn*) arrangement of this group and the *meso*-phenyl attached to the reduced bridge (the *N*-phenyl analog **3a** showed a broadening of the *N*-phenyl signals, possibly due to restricted rotation). In the epimeric phlorin **2b** (*anti*), the anisyl protons are located between δ 6.4 and 6.8.

Single crystals of *syn*-phlorin **3a** could be obtained by slow diffusion of MeOH in a solution of **3a** in $CHCl_3$. The structure could be solved† and is shown in Fig. 1. The close face-to-face arrangement of the phenyl rings was confirmed, and is illustrated by the very short distance (3.14 Å) between the closest C atoms. The rotation of the *N*-phenyl pyrrole is shown by its angles with the remaining pyrrole units: AC = 106°; AB



Reducing agent	Product
$TsNHNH_2$	**2**
$NaBH_4$	**2**
cathodic reduction (Hg)	**3**
$Na_2S_2O_4$	**3**
4	**2** + **3** (1:2)

Scheme 1

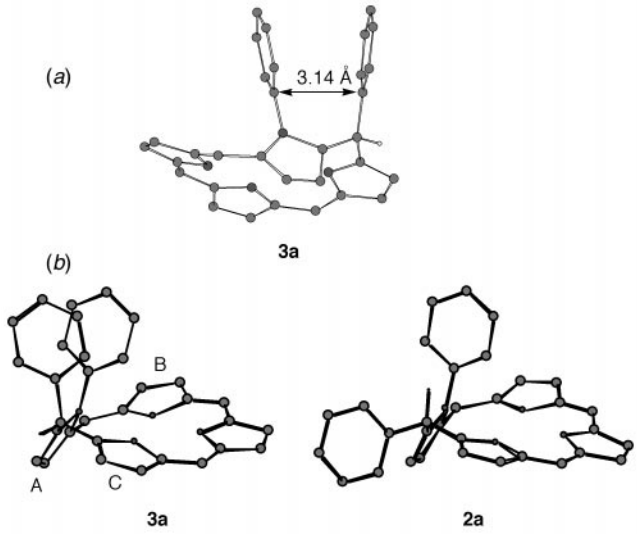


Fig. 1 (*a*) Side-view of phlorin **3a**, showing the face-to-face arrangement of the *meso*-and *N*-phenyl groups, and (*b*) comparison of phlorin **3a** with the epimeric **2a** (for the sake of clarity, three *meso*-phenyl groups and all of the hydrogen atoms except the *meso*-H are omitted).

= 130°. This last value is very similar to that found in *N*-*o*-tolyl-*meso*-tetraphenylporphyrin,[9] showing that all the deformation of the macrocycle occurred across the reduced bridge.

The use of an excess of sodium dithionite as a reducing agent in a biphasic system (water–CH_2Cl_2, 1:1) containing NMe_4Cl gave phlorins **3** from porphyrins **1** in 70% isolated yield. However, reduction of **1b** by Hantzsch ester **4** (6 equiv. in refluxing PhCl; microwave oven, 0.5 h), although quantitative, gave a mixture of both *syn* and *anti* phlorins **2b** and **3b** (1:2 ratio), Approximately 2.5 equiv. of **4** were consumed.

These results suggest two mechanistically different routes from *N*-arylporphyrins **1** to the corresponding phlorins.[10] Under electron transfer conditions (cathodic reduction, sodium dithionite) a radical anion was formed and the *meso*-bridge specifically protonated on the face opposite to the *N*-substituent. Further reduction of the radical and protonation gave **3**. Reducing agents like $NaBH_4$ or Hantzsch ester **4** are hydride donors and transferred this hydride irreversibly to the porphyrin. Tosylhydrazine reduction, although involving intermediates, might similarly begin with a nucleophilic attack of the *meso*-bridge. In these cases, steric hindrance to the approach of the reagent may govern the isomeric ratio, with the most hindered hydride donor, **4**, having difficulty approaching from the same side of the *N*-aryl group as $NaBH_4$ or tosylhydrazine, and giving *syn* **3** as the major component.

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Notes and references

† *Crystal data* for **8**: $C_{50}H_{36}N_4$, M = 692.87, monoclinic, space group $P\,1\,2_1/n\,1$; a = 17.662(2), b = 11.6074(7), c = 20.335(2) Å, β = 112.669(4)°, V = 3846(1) Å^3, Z = 4, D_c = 1.20 g cm^{-3}. A total of 29669 ± h ± k + l reflections was collected on a green crystal of dimensions 0.20 × 0.15 × 0.08 mm^3, using a KappaCCD diffractometer, graphite monochromated Mo-Kα, 2.5 < θ < 27.57, T = 294 K. 4462 unique reflections having I > 3 $\sigma(I)$ were used to determine and refine the structure. Final results: R = 0.072, Rw = 0.093, GOF = 1.524, largest peak in final difference = 1.619 e Å^{-3}. CCDC 182/1417. See http//www.rsc.org/suppdata/cc/1999/2123/ for crystallographic data in .cif format.

1 R. B. Woodward, *Angew. Chem.*, 1960, **72**, 651.
2 H. H. Inhoffen, P. Jäger, R. Mählhop and C.-D. Mengler, *Liebigs Ann.*, 1967, **704**, 188; T. Ema, M. O. Senge, N. Y. Nelson, H. Ogoshi and K. M. Smith, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 1879.
3 H. Sugimoto, *J. Chem. Soc., Dalton Trans.*, 1982, 1169; H. Segawa, R. Azumi and T. Shimidzu, *J. Am. Chem. Soc.*, 1992, **114**, 7564.
4 J. Setsune, T. Ikeda, T. Iida and T. Kitao, *J. Am. Chem. Soc.*, 1988, **110**, 6572; J. Setsune, Y. Ishimaru and T. Kitao, *Chem. Lett.*, 1990, 1351; J. Setsune, H. Yamaji and T. Kitao, *Tetrahedron Lett.*, 1990, **31**, 5057; J. Setsune, K. Wada and H. Higashino, *Chem. Lett.*, 1994, 213.
5 B. Krattinger and H. J. Callot, *Chem. Commun.*, 1996, 1341.
6 B. Krattinger and H. J. Callot, *Tetrahedron Lett.*, 1996, **37**, 7699.
7 B. Krattinger and H. J. Callot, *Eur. J. Org. Chem.*, 1999, 1857.
8 D. M. Arciero and A. B. Hooper, *Biochem. Soc. Trans.*, 1998, **26**, 385; D. M. Arciero, M. Hendrich, T. Iverson, D. Rees and A. B. Hooper. ACS National Meeting, Anaheim, March 21–25, 1999, abstr. INOR 333; see also: D. M. Arciero, A. B. Hooper, M. Cai and R. Timkovich, *Biochemistry*, 1993, **32**, 9371.
9 S. Aizawa, Y. Tsuda, K. Hatano and S. Funahashi, *Inorg. Chem.*, 1993, **32**, 1119.
10 A mechanistic dichotomy was also observed during the reductive demetallation of silver and copper porphyrins: J. A. Cowan and J. K. M. Sanders, *Tetrahedron Lett.*, 1986, **27**, 1201.

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