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New Routes from Porphyrins to Stable Phlorins. *Meso*-Alkylation and Reduction of *meso*-Tetraphenyl- and Octaalkylporphyrins.

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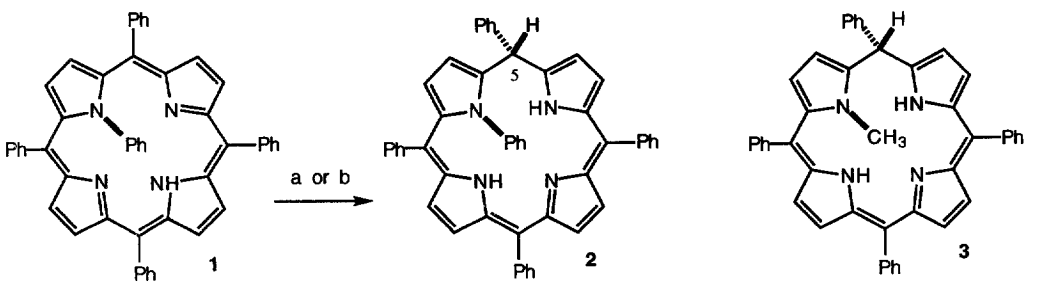
Abstract: Borohydride reduction of N-alkyl or N-arylporphyrins gave the corresponding 5-H-phlorins. 5-Butyl-*meso*-tetraphenylphlorin as well as 2-butyl-*meso*-tetraphenylchlorin were obtained on addition of *n*-butyllithium to *meso*-tetraphenylporphyrin free base.

Phlorins[1-5] are non-aromatic tetrapyrrolic macrocycles isomeric to chlorins (dihydroporphyrins), but reduced at a bridge (*meso*) position. Although the oxidation of phlorins to porphyrins is often a fast reaction, we recently isolated[6] the first stable monocyclic phlorin free base, 5,21-dihydro-5,10,15,20,22-pentaphenyl-porphyrin **2**, by reduction ($TsNHNH_2$ in refluxing toluene or pyridine) of the corresponding N-phenyl-*meso*-tetraphenylporphyrin **1** (N-phenylTPP). The ease of formation of this compound was clearly related to a steric strain release that was the consequence of the tilting of the N-phenyl-pyrrole ring[6]. Here we describe additional routes to stable N-substituted phlorins and show that the addition of organometallics to non-N-substituted unactivated porphyrins may also lead to phlorins as well as to chlorins.



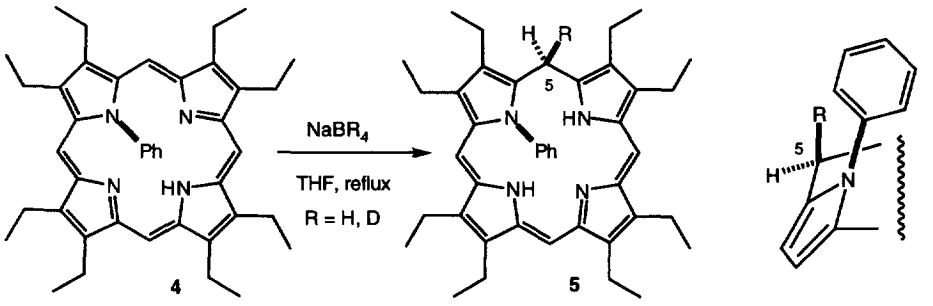
a) $TsNHNH_2$, toluene
b) $NaBH_4$, THF-EtOH, reflux

The reduction of **1** to **2** with tosylhydrazine is a multistep sequence (addition, elimination, loss of N_2). Since the first and crucial step must be a nucleophilic addition to a *meso* position triggering the rotation of the N-phenyl-pyrrole, a hydride donor should perform all in one step. This assumption proved to be correct and reaction of **1**

with $NaBH_4$ in refluxing THF-ethanol (2:1) gave **2** in almost quantitative yield. The corresponding zinc complex was also transformed into the phlorin free base when treated with $NaBH_4$.

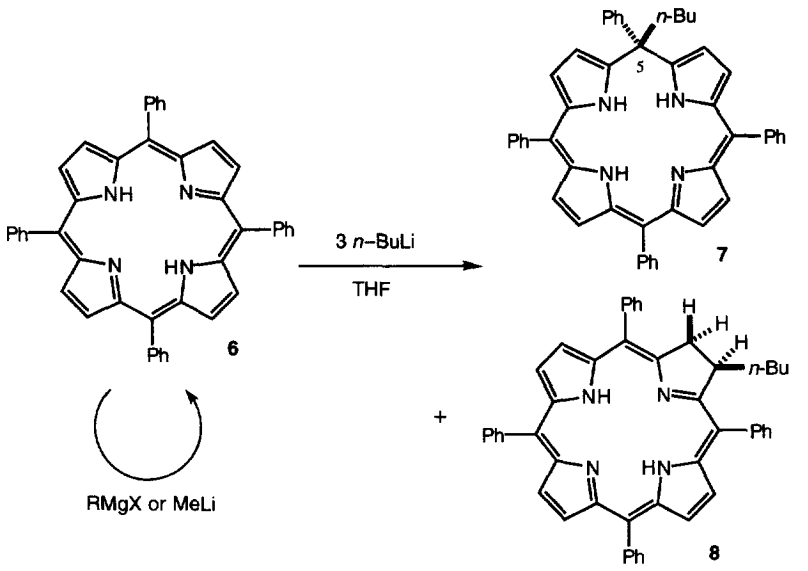
This reduction ($NaBH_4$ or tosylhydrazine) could also be extended to N-alkylporphyrins: N-methylphlorin **3** was obtained in 62% yield (/transformed porphyrin; crystallized) from N-methylTPP and $NaBH_4$. The ^1H NMR data[7] of **3** are very similar to that of **2**: *meso* proton at 4.92 ppm (**2**: 4.34 ppm), pyrrolic protons between 6.18 and 7.26 ppm (**2**: 6.16 to 6.98 ppm). The N-methyl group is shifted from -4.10 ppm in N-methylTPP to 2.79 ppm. The reduction of the less distorted[8] N-methylTPP is much slower than that of N-phenylTPP. This is also illustrated by the fact that, when treated with tosylhydrazine and base, N-methylTPP gave a mixture of aromatic dihydro- and tetrahydroTPP's: the formation of diimide and subsequent β-reduction competed efficiently with the direct *meso*-addition of tosylhydrazine (under the same condition N-phenylTPP gave only the corresponding phlorin).

Both sets of conditions (tosylhydrazine or $NaBH_4$) allowed us to extend the reduction to the octaalkylporphyrin series. Reduction of N-phenyloctaethylporphyrin **4** (N-phenylOEP) gave the corresponding phlorin **5**, which was significantly less stable than its TPP counterpart. As with **2** the N-phenyl NMR signals[9] shifted from high field to a normal position, confirming the loss of aromaticity. The 5-*meso*-CH_2 group appears as two widely separated AB doublets (4.54 and 2.94, J = 16.5 Hz), the high field one being reasonably attributed to the pseudo-axial proton, which is close to the N-phenyl group, as shown by the X-ray data from **2**[6].



Reduction of N-phenylOEP **4** with $NaBD_4$ gave a monodeuterated product in which the pseudo-axial H is almost quantitatively labelled. This is in agreement with the results of Setsune *et al.*[2] who found the same axial specificity in the addition of nucleophiles to bridged porphyrins.

To prepare "blocked" phlorins we tested the reaction of organometallics with porphyrin bases. N-substituted porphyrins were either inert (RMgX) or produced complex mixtures (RLi), from which phlorins (to be described elsewhere) were isolated in poor yield. At this stage we decided to use simpler porphyrins, unsubstituted at nitrogen, expecting that the double deprotonation to the lithium complex of the porphyrin[10] would enhance the selectivity (or possibly inhibit further addition). Reaction of H_2TPP **6** with MeLi (3 eq.) led to a dramatic color change from violet (starting porphyrin) to green but only to the recovery of the starting material after work-up (the same result was observed with RMgX). On the other hand, use of *n*-BuLi (3 eq.; -78° → -20°C) gave two major products (green 26% **7**, brown **8** 18%; crystallized after chromatography), most H_2TPP **6** being consumed (6% recovered).



The brown compound **8** retained an aromatic conjugated system and all its data[11] were in agreement with a chlorin structure. Although β-addition of nucleophiles to porphyrins is a known reaction[12], it is, to our knowledge, the first example of such a reaction at an unactivated position.

The less polar green product is phlorin **7** (N-H positioned arbitrarily). Its stability in solution in the presence of dioxygen is moderate and it oxidized to a series of polar pigments still under study. However this phlorin can be kept at room temperature as stable crystals and could be characterized by NMR[13] and elemental analysis. The NMR data for phlorin **7** show two AB systems for the pyrrolic protons, as well as a signal corresponding to shielded *ortho* phenyl protons (6.31 ppm, 2H) and a deshielded 5'-butyl-CH_2 (3.29 ppm). This suggests a substantial folding of the macrocycle, the 5-phenyl group being placed above the planes of two pyrroles and the 5'-butyl CH_2 close to the pyrrole planes.

The addition of Grignard reagents to activated *meso*-formyloctaethylporphyrins (free base or zinc complex) was described very recently[5]. A phlorin intermediate of moderate stability could be observed, similar to an intermediate earlier postulated by Setsune *et al.*[14] on addition of an aryllithium reagent to a rhodium(III)porphyrin. In our case the clean reaction between *n*-BuLi and H_2TPP did not require any activating group (M(III), -CHO).

Extension of this addition to sterically more demanding reagents gave less satisfactory results. Under the same conditions, reaction of H_2TPP with *sec*-BuLi gave complex mixture of chlorins and non-aromatic products, but no phlorin could be characterized so far, while *t*-BuLi only led to a low conversion (≤ 30%) and multiaddition products.

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11. Chlorin **8** (selected data). UV-vis. (CH_2Cl_2; λ_{max} (nm, ε)): 420 (122000), 520 (9500), 546 (7000), 598 (4200), 650 (17900). ^1H NMR ($CDCl_3$): 8.58, 8.57 (2d, 1+1H, pyrrole), 8.42 (s, 2H, pyrrole), 8.3-7.6 (m, 22H, phenyl+pyrrole), 4.70 (dddd, 1H, 2-H, J = 10, 8.5, 1.5, 1 Hz), 4.39 (dd, 1H, 3-H, syn/butyl, J = 17.5, 1.5), 3.90 (dd, 3-H anti/butyl, J = 17.5, 8.5 Hz), 3.28, 0.90, 0.55 (m+m+t, 2+4+3H, butyl).
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13. Phlorin **7** (selected data). UV-vis. (CH_2Cl_2; λ_{max} (nm, rel. intensity)): 420 (broad, 1.00), 676 (broad, 0.349). ^1H NMR ($CDCl_3$): 7.9-7.5 (m, 15H, phenyl), 7.41 and 7.20 (2d, 2+2H, J = 4.9 Hz, pyrrole), 7.13 and 7.07 (2d, 2+2H, J = 3.9 Hz, pyrrole), 6.88 (m, 3H, 5-phenyl *m*+*p*-H), 6.31 (br d, 2H, 5-phenyl *o*-H), 3.28 (t, 2H, 5'-CH_2), 1.5 (m, 4H, $2CH_2$), 0.98 (t, 3H, CH_3).
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