

## A Rational Step-by-Step Preparation of a Chlorin from Linear Tetrapyrroles

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**Abstract:** Formation of porphodimethene **2** by condensation of pyrromethanes **3** and **4**, metalation with Zn(OAc)<sub>2</sub> under neutral conditions and heating to 55°C for 1 hour in chloroform produces chlorin **5** in 27% yield.

Recently, many syntheses of dihydroporphyrins (chlorins) have been reported.<sup>1-4</sup> This flurry of activity is a reflection of their potential both as photodynamic therapeutic agents<sup>1a-d</sup> and as biomimetic models of the green hemes (such as heme d<sup>2</sup> and sulfheme<sup>3</sup>) and photosynthetic centers.<sup>4</sup> The reactions proceed with modest yields, require several steps and generally involve conditions that are highly acidic or basic, or require high temperatures. However, these chlorin preparations are all variations on the same theme, *i.e.*, the transformation of a parent porphyrin into the corresponding dihydroporphyrin. To date, no general method has been devised in which a chlorin is built in the rational, step-by-step fashion from linear tetrapyrroles as now commonly employed in porphyrin synthesis.<sup>5</sup> We would like to report on our initial results at the establishment of a method that proceeds under mild conditions and shows surprising regioselectivity.

Closs<sup>6</sup>, Buchler<sup>7</sup> and Whitlock<sup>8</sup> have demonstrated that an equilibrium exists between the anion of a metalated phlorin (derived from the corresponding porphyrin) and metalated chlorin, and is dependent on base concentration, temperature, solvent, and what metal ion is complexed to the macrocyclic core. Since these factors are controllable, we felt that the preparation from linear tetrapyrroles of a metalated phlorin might constitute a general entry into the chlorin macrocycle. Further, the phlorin anion seemed to be the equivalent of the monoanion of a porphodimethene and porphodimethenes can be prepared in the MacDonald condensation of pyrromethanes; thus, a direct route to chlorins from pyrrole precursors seemed feasible.

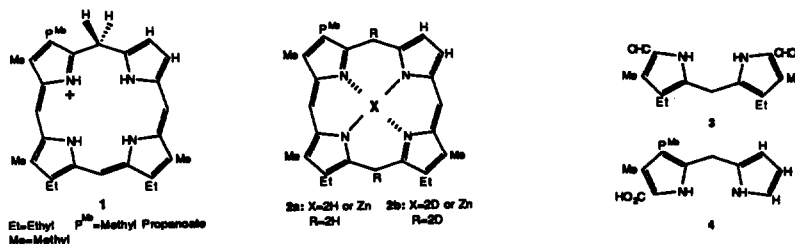


Fig. 1.

We found that the fairly typical condensation conditions of 5 equivalents of toluenesulfonic acid in chloroform at room temperature produced the porphodimethene intermediate, which was stable to the reaction conditions.<sup>9</sup> However, we modified the MacDonald procedure by utilizing the dilution principle<sup>10</sup> for the addition of the two pyrromethanes 3<sup>11</sup> and 4,<sup>12a,b</sup> and did not add any metal to the reaction mixture until after neutralization with a bicarbonate wash. After the wash, besides polymeric material, the reaction exhibited an equilibrium mixture of mostly phlorin 1 (olive green, visible spectrum: 430 nm peak and broad peak around 750 nm) and porphodimethene 2a (red, visible spectrum: broad peak at 460 nm). Chromatography (chloroform, neutral alumina, grade III) of this mixture resulted in removal of much of the polymeric material and a shift of the equilibrium to the phlorin species.

Metalation of the phlorin 2a (chloroform, saturated Zn(OAc)<sub>2</sub> in methanol, 55° C) was complete after 5 minutes as evidenced by the change in the visible spectrum from phlorin to metalated porphodimethene seen in Figure 2A (emergence of 470 nm peak with a clean isobestic point at 435 nm). After 15 minutes, an unexpected conversion of the metalated porphodimethene to metalated chlorin occurred as evidenced by the appearance in the visible spectrum of a Soret peak at 400 nm, an absorption peak at 620 nm, and a concomitant decrease in the porphodimethene absorption peak at 470 nm (Figure 2B). Complete conversion to metalated chlorin took 1-1.5 hours. Examination of the <sup>1</sup>H NMR spectrum<sup>12c</sup> (Figure 3A) of the demetalated chlorin (trifluoroacetic acid, 5 minutes, 0° C) detailed four meso-proton resonances, no aromatic β-hydrogens and one resonance at 4.67 ppm (4H) clearly indicative of the presence of only regioisomer 5a.<sup>12b,c</sup> Force field calculations<sup>13</sup> show this regioisomer is *not* the most thermodynamically stable reduced ring. While rearrangement under kinetic control<sup>14</sup> would be expected to produce regioisomer 5a in excess over the other three possible reduced-ring isomers, formation of only 5a is remarkable (HPLC analysis shows 5a to be 98% of the chlorin mixture, with 1-2% of other unidentified chlorin isomers). Yields of 24-27% of chlorin were common when the condensation reaction ran 8-9 hours, the alumina column was bypassed and instead the neutralized crude reaction mixture was metalated directly. The major by-product was porphyrin (2.5-5% of the product mixture), and was easily separated from chlorin with column chromatography (neutral alumina, grade III, eluted with benzene).

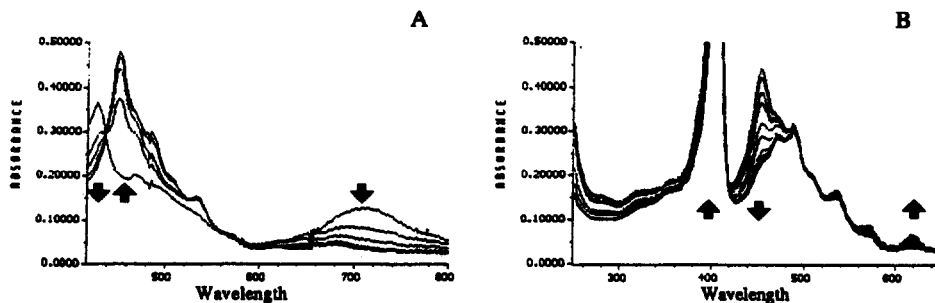


Fig. 2. (A) Visible spectrum showing the formation of metalated porphodimethene from phlorin over 5 minute period (arrows indicate increasing and decreasing absorption with time). (B) Visible spectrum showing the formation of metalated chlorin and concomitant loss of metalated porphodimethene over 15 minute period.

That rearrangement occurred without the addition of base, or the apparent formation of a monoanion of the metalated porphodimethene, was surprising. When the rearrangement was followed by visible spectrophotometry, no absorption at 800 nm (phlorin anion<sup>6,8</sup>) was ever observed. Indeed, no chlorin was

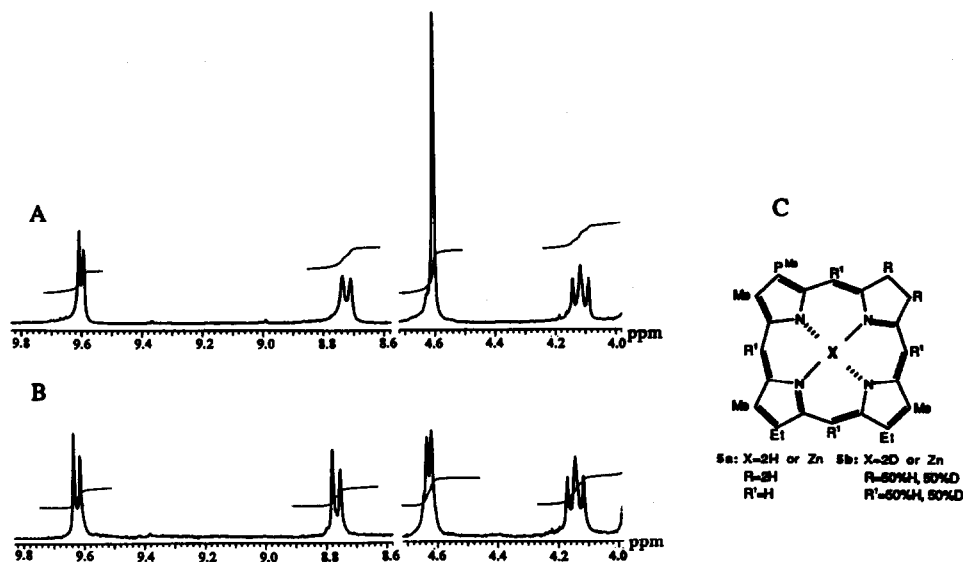


Fig. 3. (A) Partial <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) of chlorin 5a, showing meso-protons, reduced ring β-protons and propanoate methylene for integration comparison. (B) Same partial spectrum of 5b. (C) Structures of 5a and 5b.

produced when the cuvette solution was made slightly basic with triethylamine (nor was rearrangement observed when the cuvette solution was made slightly acidic with acetic acid). When excess Zn(acac)<sub>2</sub><sup>15</sup> (with a more basic ligand than acetate) was added to the neutralized reaction mixture, metalation was immediate but no rearrangement took place. Further experiments demonstrated that the transformation 2a to 5a was slow to nonexistent when 1-1.5 equivalents of Zn(OAc)<sub>2</sub> were used, but rearrangement was done within the one hour time frame when more than two equivalents were used. However, when the saturated Zn(OAc)<sub>2</sub>/methanol solution was removed and only the metalated porphodimethene in chloroform was heated to 55°C, rearrangement occurred in a normal manner. Finally, rearrangement of tetradeutero 2b<sup>16,17</sup> in chloroform at 55°C resulted in the deuteration of 50% of *all* meso-carbons and 50% of the β-carbons in the reduced ring (presumably with formation of chlorin 5b<sup>12b</sup>) as determined from proton NMR (Figure 3B). The data is consistent with the possibility that acetate was acting as a fifth, axial ligand that aided in the shifting of protons about the periphery of the ring while it rotated around the metal, in a similar manner to the "guanidine-like" base used for rearrangement of porphyrinogen to corphin detailed in Eschenmoser's eloquent studies on the biosynthesis of vitamin B<sub>12</sub>.<sup>18</sup>

Work to further elucidate the mechanism of this rearrangement, its generality to other ring systems and the stereoselectivity of ring reduction is currently in progress.

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- (a) **4** is prepared in 55% yield by the reaction of pyrrole with benzyl 5-acetoxymethyl-4-(2-methoxycarbonyl-ethyl)-3-methylpyrrole-2-carboxylate<sup>17</sup> followed by hydrogenation.

(b) All new compounds gave satisfactory spectroscopic and elemental analysis.

(c) Chlorin **5a**. m.p. (uncorrected): 203-205° C. Visible: (CH<sub>2</sub>Cl<sub>2</sub>)  $\lambda_{\max}$  (e) 388 (158900), 496 (10703), 522 (3446), 544 (1625), 594 (3716), 618 (4150), 648 (41107).  
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  9.61, 9.59 (s, 2H,  $\gamma,\delta$ -H), 8.74, 8.71 (s, 2H,  $\alpha,\beta$ -H), 4.60 (s, 4H, 3,4-H), 4.12 (t, 2H, J=8.01 Hz, 2-CH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>), 3.93, 3.83 (q, 4H, J=7.59 Hz and J=7.53 Hz, respectively, 6,7-CH<sub>2</sub>CH<sub>3</sub>), 3.70, 3.47, 3.37, 3.33 (s, 12H, 1,5,8-CH<sub>3</sub>, CO<sub>2</sub>CH<sub>3</sub>), 3.10 (t, 2H, J=8.01 Hz, 2-CH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>), 1.78-72 (m, 6H, 6,7-CH<sub>2</sub>CH<sub>3</sub>), -2.35 (s, 2H, NH).
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- Tetradecuteration of both methylene positions of a porphodimethene using Toluenesulfonic acid-d is known.<sup>17</sup> Thus, MacDonald condensation of **3** and **4** with toluenesulfonic acid-d<sub>4</sub> in CHCl<sub>3</sub>, followed by a D<sub>2</sub>O/ bicarbonate wash, metalation with a saturated solution of Zn(OAc)<sub>2</sub>·xD<sub>2</sub>O in CH<sub>3</sub>OD, followed by a second D<sub>2</sub>O wash, removal of all solvent, then reintroduction of CHCl<sub>3</sub> and warming to 55° C for one hour yielded **5b**.
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