SOME NEW PORPHODIMETHENE CHEMISTRY: SYNTHESIS OF *MESO*-FORMYLPORPHYRINS§

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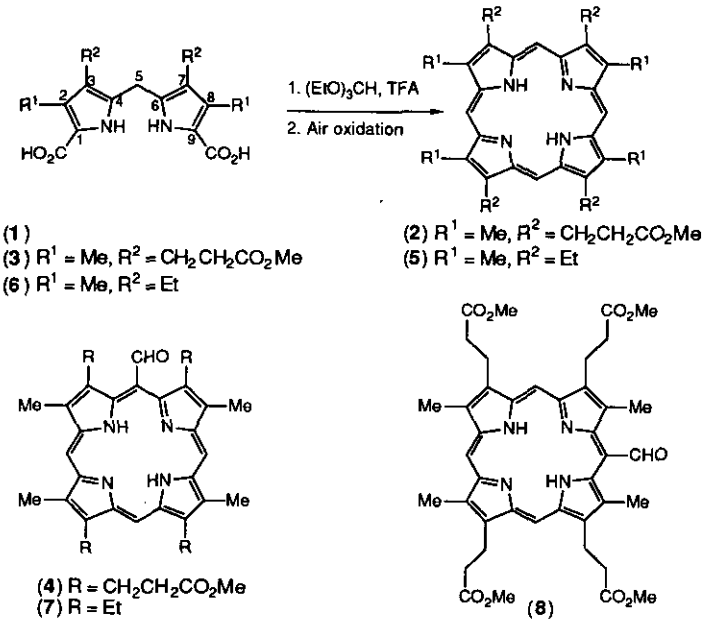
Abstract - Treatment of dipyrromethane-1,9-dicarboxylic acids with triethyl orthoformate and trifluoroacetic acid gives the expected symmetrically substituted porphyrin, along with small amounts of *meso*-formyl and *meso*-diformyl-porphyrins. The 5,15 regioselectivity of the formyl groups in the disubstituted product and NOE experiments suggest that serendipitous formylation takes place at the intermediate porphodimethene stage.

One of the most direct methods for synthesis of symmetrically substituted porphyrins from dipyrromethanes involves the treatment of a dipyrromethane-1,9-dicarboxylic acid (**1**), or the corresponding 1,9-di-unsubstituted derivative, with an orthoformic ester in the presence of acids such as trifluoroacetic acid (TFA).[1,2] We recently chose this method as an efficient route for preparing large quantities of coproporphyrin-II tetramethyl ester (**2**) from the dipyrromethanedicarboxylic acid (**3**), triethyl orthoformate, and TFA. Along with the expected product (**2**) (20 % yield) we also observed a small amount (2 %) of a *meso*-monoformylporphyrin porphyrin (**4**). Similar results were obtained when we attempted to prepare etioporphyrin-II (**5**) by the same route from dipyrromethane (**6**); in this case, along with etioporphyrin-II (**5**) (16 %) a 1.5% yield of the formylporphyrin (**7**) was isolated. Though we cannot reasonably regard the low yields of porphyrins (**4**) and (**7**) to constitute a viable synthesis of *meso*-formylporphyrins, we felt that interesting chemistry had taken place and therefore decided to complete an investigation of the origin of these novel and unexpected products.

§ Dedicated to Professor Alan R. Katritzky, FRS, on the occasion of his 65th birthday.



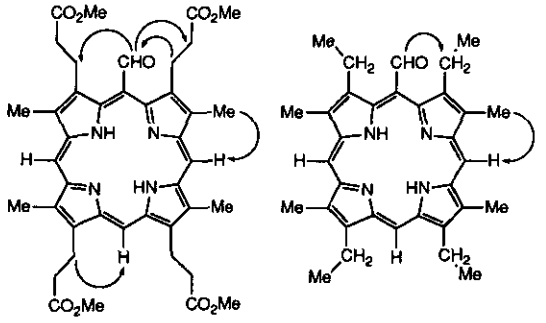
(1)
(3) R^1 = Me, R^2 = $CH_2CH_2CO_2Me$
(6) R^1 = Me, R^2 = Et

(2) R^1 = Me, R^2 = $CH_2CH_2CO_2Me$
(5) R^1 = Me, R^2 = Et

(4) R = $CH_2CH_2CO_2Me$
(7) R = Et

(8)

Conclusive proof that the formyl group is located between the sterically congested propionates of **2** or the ethyls of **6** was obtained from nuclear Overhauser enhancement (NOE) difference spectra. Selected enhancements are shown in Figure 1; the observed pattern of NOEs completely precludes the possibility that the formyl group in **2** or **6** is on a meso position between the methyl substituents. To illustrate the quality of the spectra obtained, the 300 MHz proton nmr spectrum of **2** in $CDCl_3$, together with a NOE difference spectrum obtained after irradiation of the α-methylene propionate resonance at 4.04 ppm is shown in Figure 2. Enhancements to the formyl proton (12.62 ppm), adjacent methyl protons (3.52 ppm), and the β-methylene protons of the propionate chain (3.06 ppm) are readily apparent.



(4) (7)

Tail of arrow shows irradiated proton.

Figure 1: NOE connectivities for porphyrins (**4**) and (**7**).

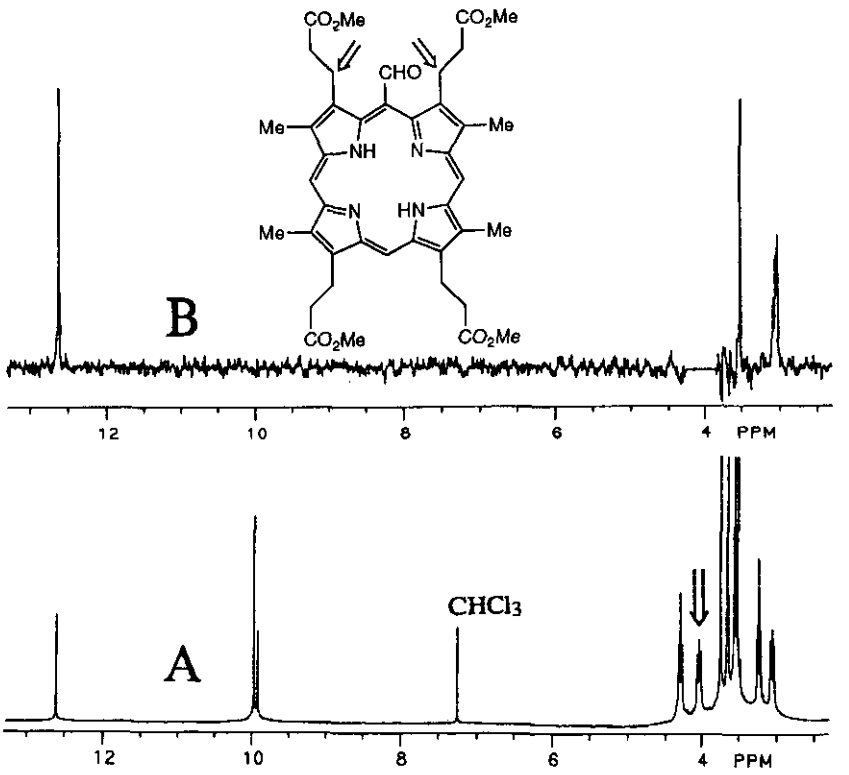
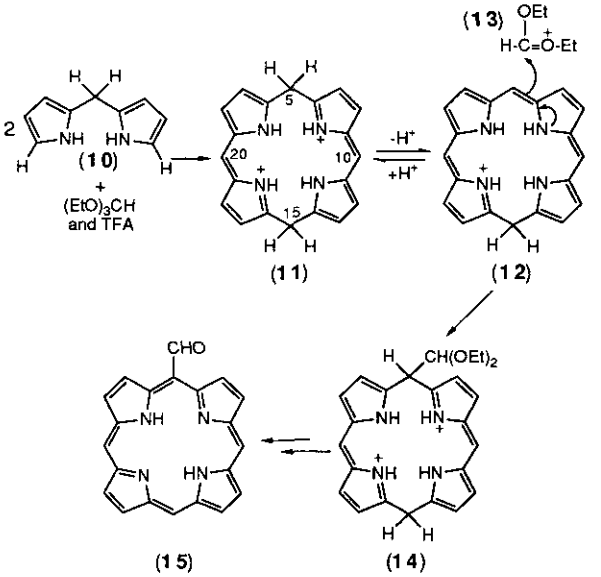


Figure 2: 300 MHz Proton nmr spectrum, in $CDCl_3$, of: A, formylporphyrin (**4**); B, NOE difference spectrum after irradiation (⇓) at 4.04 ppm.

The formation of *meso*-formylporphyrin, particularly with the formyl group sited regioselectively between the propionic (**4**) or ethyl (**7**) side chains at the *most sterically congested* position, suggested the involvement of a novel process. Prior to establishment of the structure (**4**) using the NOE techniques, we suspected that the product was compound (**8**), assuming the coproporphyrin-II tetramethyl ester had suffered an unexpected formylation at the least hindered *meso*-position; however, such formylation reactions are normally encountered only with metal complexes such as those of copper, nickel, or iron. We also considered the possibility of self-condensation of two moles of a formyldipyrromethane (or its acetal), followed by intramolecular migration of the extra formyl equivalent, but that would still have resulted in the new formyl group being sited between the methyls rather than propionates. The regioselectivity in the experiments with coproporphyrin-II tetramethyl ester was therefore confirmed by preparation of **7**.

It was further established that formylation of an intact porphyrin was not taking place by submitting, for example, coproporphyrin-II tetramethyl ester (**2**) or the sterically unhindered octamethylporphyrin (**9**) (see later) to reaction

conditions identical with those employed in the cyclization reaction; no *meso* formylation products were observed in either case.

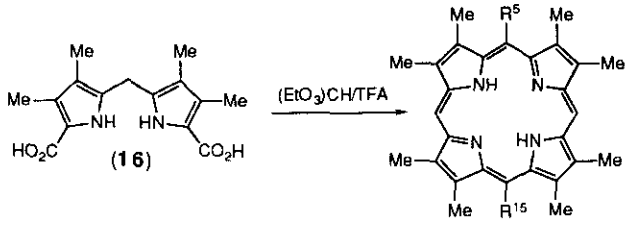


Scheme 1: Proposed mechanism for formation of regioselectively *meso*-formylated porphyrin (**15**) from dipyrromethane (**10**); peripheral substituents have been omitted.

For the novel *meso*-formylation reaction, we propose the mechanism shown in Scheme 1. Condensation of the dipyrromethane (**10**) (or its corresponding 1,9-dicarboxylic acid) should give the porphodimethene (**11**); such compounds have previously been shown[3] to undergo deuteriation at the opposite macrocyclic methylenes owing to the facile acid-base equilibrium between **11** and **12**. Use of the activated orthoformate species (**13**) in place of a proton would give rise to **14** which, after hydrolysis and oxidation to the porphyrin level (in any order) would give the formylporphyrin (**15**). In principle, since deuteriation of the porphodimethene takes place at both macrocyclic methylenes, it should be possible to obtain a diformylporphyrin in the triethyl orthoformate/TFA reaction, but these formyl groups should be only disposed on "opposite" (5,15) [rather than "adjacent" (5,10) carbons].

We therefore extended our study to the synthesis of octamethylporphyrin (**9**). When the dipyrromethane (**16**) was treated with triethyl orthoformate and TFA under the normal conditions, octamethylporphyrin (**9**) plus two other (more polar) porphyrins were obtained. These compounds were identified as 5-formyloctamethylporphyrin (**17**) (1.6% yield) and 5,15-diformyloctamethylporphyrin (**18**) (1.3 %); no attempt has been made to optimize the yields of these last compounds. The structure of **18** was obvious from the mass spectrum and proton nmr integration, both of which indicated diformylation, while the symmetry exhibited in the proton nmr spectrum

which exhibited only four singlet peaks [in $CDCl_3$ at 300 MHz, δ, 12.34 (s, 2H, CHO), 10.20 (s, 2H, 10- and 20-meso-H), 3.25 (s, 12H, 4 x Me), 3.00 (s, 12H, 4 x Me)] confirmed 5,15-disubstitution. As would be expected on the basis of the mechanism in Scheme 1, the 5,15-diformyl product was the *only* disubstituted one obtained.



(**9**) $R^{5,15}$ = H
(**17**) R^5 = CHO, R^{15} = H
(**18**) $R^{5,15}$ = CHO

The MacDonald-type synthesis of porphyrins[4] using orthoformates[1] is usually carried out in the presence of oxygen so that the intermediate porphodimethene (**11**) is oxidized, in situ, to porphyrin. In principle, therefore, it should be possible to increase the yield of the monoformyl- and diformylporphyrins by extending the lifetime, in solution, of the porphodimethene (i.e. by preventing its oxidation to porphyrin). When, in a preliminary investigation, the reaction was carried out, in the dark and with rigorous exclusion of oxygen for 24 hours, followed by aerial oxidation in the normal way, a 3% yield of the formylporphyrin (**4**) was obtained. We suggest that further optimization of this approach should yield an efficient method for preparation of 5,15-disubstituted porphyrins useful for a number of purposes (e.g. for strapping side-chains over the center of a porphyrin or metalloporphyrin). Exhaustive meso-formylation of metalloporphyrins normally gives[5] both the 5,10- and 5,15-disubstituted porphyrins, rather than only the 5,15-products observed here. Replacement of (**13**) with other electrophiles should lead to development of additional procedures for regioselective functionalization of the porphyrin core. These studies are in progress.

ACKNOWLEDGMENTS

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