A New Look into the Rothemund *meso*-Tetraalkyl and Tetraarylporphyrin Synthesis

A. M. d'A. Rocha Gonsalves* and Mariette M. Pereira

Departamento de Química, Faculdade de Ciências e Tecnologia
Universidade de Coimbra, P-3000 Coimbra, Portugal

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meso-Tetraalkylporphyrinogens are easily formed and unexpectedely stable compounds. Only through forced oxidation can they efficiently be converted into porphyrins. *meso*-Tetraphenylphlorin was trapped as an intermediate in the Rothemund *meso*-tetraphenylporphyrin synthesis.

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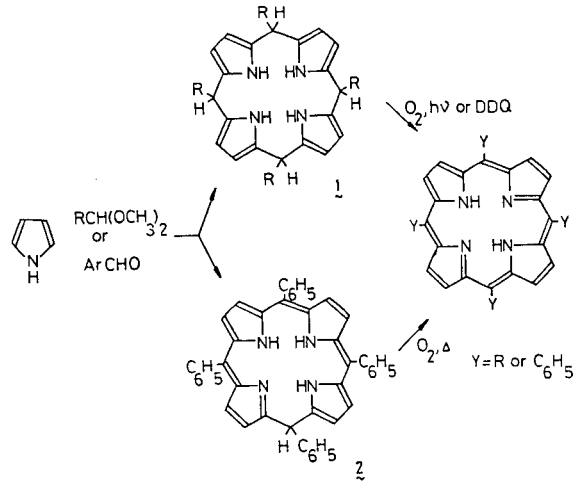
Interest in widening the applicability of the Rothemund type porphyrin synthesis has increased recently [1]. Despite the claims of breakthroughs there have been no real improvements with respect to the challenge put by the synthesis of *meso*-tetraalkylporphyrins. From our experience published methods lead to smaller yields than claimed and are unreliable. The known and potentially undisclosed properties and interest of *meso*-alkylporphyrins and hydroporphyrins together with the ready availability and low price of starting materials for such compounds make it desireable to sort out the reasons that have made the synthesis of such compounds so difficult.

Results and Discussion.

While it is known [2] and keeps being shown [3] that porphyrinogens are easily formed, we found that the situation is not different when an aldehyde or preferably the corresponding acetal is made to react with pyrrole in the presence of a catalytic amount of a strong acid. It was to be expected that this reaction might lead directly to the formation of porphyrin but we found that it is not so due to difficulties in overcoming the porphyrinogen state. *N,N',N'',N'''*-tetraalkylporphyrinogens are stable to oxidation owing to their non-planar structure [2b]. Normal sterically crowded porphyrinogens are also stable enough to be isolated [4], and in some cases they require special conditions to be fully oxidized [5]. On these grounds one does not expect *meso*-tetraalkylporphyrinogens, in particular tetramethylporphyrinogen, to be stable. However our results show that such porphyrinogens and their intermediate oxidation states up to the porphyrin level are particularly stable to oxidation. It was known [6] that in the mechanism of the *meso*-tetraphenylporphyrin Rothemund synthesis the oxygen-oxidation is the rate determination step but it was never suspected [7] that the poor success of previous attempts to prepare *meso*-tetraalkylporphyrins originated exclusively in the difficult oxidation of the porphyrinogens.

We found that when pyrrole and a dimethylacetal of an alkylaldehyde are condensed at low temperature in a mixture of benzene-acetic acid (50:50) in the presence of a catalytic amount of a strong acid in an inert atmosphere, the reaction gave little degradation products but the quantity of porphyrin obtained was extremely small even after long subsequent exposure to the air. When the reaction is done in carbon tetrachloride [8] preferably in an inert atmosphere, nmr evidence (Figure 1) showed us that the reaction goes easily to the porphyrinogen stage [9] and that this compound is formed in high yield. Observation of the nmr also suggested that the most likely mechanism of the Rothemund reaction involves the formation of the pyrromethane, after which two units of these condense in a MacDonald type cyclization.

Scheme 1



Subsequent oxidation of the porphyrinogen so prepared by either photo or chemical oxidation [10] allowed us to prepare several *meso*-tetraalkylporphyrins in considerably improved yields (Table 1), and free from any chlorin contamination as happens in previous claims [12]. The photooxidation route usually leads to lower yields certainly as a consequence of photodegradation of the porphyrin. In the *meso*-tetramethylporphyrin case the extremely low solubility of the compound leads to very big losses in the work up following chemical oxidation; the photooxidation route

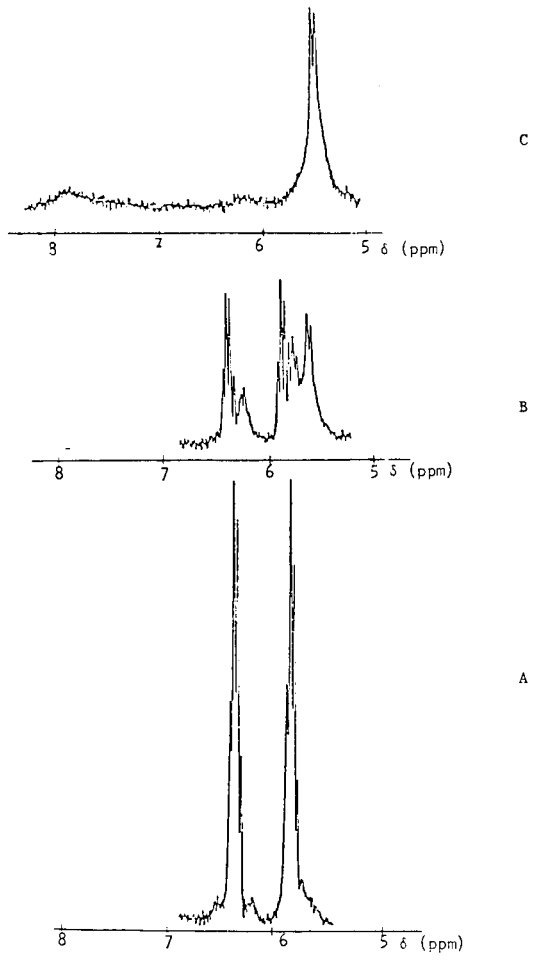


Figure 1. Pyrrolic proton resonances evolution during the Rothemund cyclization; A, starting of reaction; B, after 2 hours; C, after 16 hours.

gives better yields here.

The reported observations widen the recently established concept [3] of the high favorability of porphyrinogen formation. The fundamental novelty comes from the fact that ours is a new class of stable porphyrinogens whose stability can not be attributed to simple steric constraints.

Table 1

Porphin	Isolated yields % Photooxidation	Chemical oxidation
	Trace	—
meso-Tetramethylporphyrin	8	—
meso-Tetraethylporphyrin	5	11
meso-Tetra-n-propylporphyrin	10	18
meso-Tetra-iso-propylporphyrin [11]	0	5
meso-Tetra-iso-butylporphyrin	8	15.9
meso-Tetrabenzylporphyrin [11]	6.4	17
meso-Tetra-n-undecylporphyrin	9	8.5

That the observed stability is a property characteristic of *meso*-alkylporphyrinogens is clear from the fact that when pyrrole and benzaldehyde are made to react under the experimental conditions reported here in presence of air, the product goes smoothly first to porphomethene and subsequently to a green compound that we believe from the accumulated evidence to be *meso*-tetraphenylphlorin (**2**) [13]. This is the first time that *meso*-tetraphenylphlorin is identified as an intermediate in *meso*-tetraphenylporphyrin synthesis, thus confirming Alder's hypothesis [13] and contradicting Dolphin's apparently unfavourable evidence [4].

We believe that making use of the present results the way is open to the preparation of a wide pattern of *meso*-substituted hydroporphyrins with stabilities spanning over a wide range. As shown in Scheme 1, *meso*-alkyl substituted compounds are relatively stable at the porphyrinogen level while the *meso*-aryl compounds show stability at the dihydroporphyrin level. These hydroporphyrins are compounds which may prove to be of great interest not only for the further understanding of the role of hydroporphyrins in biological functions, but also for the preparation of useful model systems for photochemical, electrochemical and biochemical studies. We intend to exploit our results for further developments into these areas.

EXPERIMENTAL

Proton nmr spectra were determined with the use of a Varian EM360L (60MHz) spectrometer.

Porphyrinogen.

As a general procedure pyrrole (7.2×10^{-3} mole) is added to the required dimethylacetal (7.2×10^{-3} mole) in carbon tetrachloride (20 ml) in the presence of a catalytic amount of TFA (0,2 ml). The solvent was purged with argon and the reaction mixture was warmed in a water bath at 60° for 16 hours. A standard-work up yielded the crude porphyrinogen.

Porphyrin.

Photooxidation Method.

The crude porphyrinogen was dissolved in benzene acetic acid (8:2, 1000 ml) and photooxidized using 8 fluorescent 8W Philips lamps until the Soret band reached its maximum value (*ca.* 3 hours). A standard work up followed by chromatography in neutral alumina (Woelm, grade II) eluting with chloroform gave the porphyrin which was crystallized in chloroform/methanol. Yields shown in Table 1.

Chemical Oxidation Method.

The crude porphyrinogen was dissolved in chloroform (100 ml) and heated to 60°. One equivalent of DDQ or chloranil in benzene (100 ml) is added all at once. The temperature is maintained at 60° for 30 minutes. Work up as before gave yields as shown in Table 1.

The products were identified by visible and nmr spectroscopy, and melting points. All data in agreement with values found in literature.

Acknowledgement.

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[7] Electrophilic attack at the β-positions and formation of noncyclic oligomers were considered responsible for the failure of this method to yield porphyrins (check ref 2).

[8] Chloroform can be used instead.

[9] It is known that the chlorinated solvents do not favour the oxidation step (check ref 4).

[10] Both dicyanodichloroquinone and *p*-chloranil proved to be efficient.

[11] This is a new compound which contrary to other *meso*-tetraalkylporphyrins shows an *etio*-type visible spectrum.

[12] I. Tabushi, K. Sakai and K. Yamamura, *Tetrahedron Letters*, 1821 (1978).

[13] The compound is stable enough to stand isolation by column chromatography but could not be purified for full characterization. However, its visible (λ max 423, and 630 nm) and nmr (β-H 7,2 δ (s, broad base), Ph-H 7,65 δ (m)) spectroscopic characteristics fit to the assigned structure.

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