A NEW SYNTHESIS OF OCTAARYLPORPHYRIN: NATURALLY OCCURRING PORPHYRIN MIMICS

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Octaarylporphyrins were obtained in high yields by cyclization of 3,4-diarylpyrrole with formaldehyde and subsequant DDQ oxidation. The reaction intermediates identified as porphyrinogen and porphodimethene have been characterized spectroscopically.

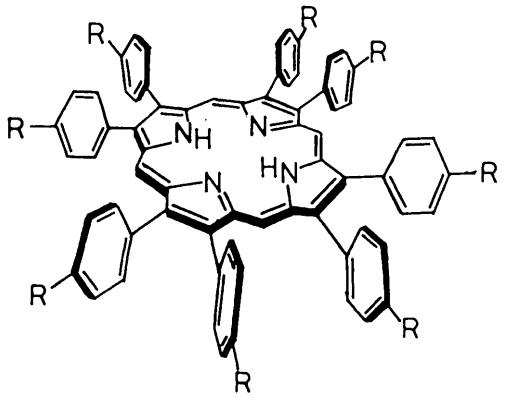
KEYWORDS octaarylporphyrin; diarylpyrrole; porphyrinogen; porphodimethene; autoxidation

meso-Substituted tetraphenylporphyrin (TPP) is one of the most important and widely used models for the study of porphyrin chemistry. However, naturally occurring porphyrin (e.g., protoporphyrin IX), unlike TPP have substituents at β-pyrrole positions. Octaethylporphyrin (OEP) is a symmetrically β-substituted porphyrin which more closely resembles naturally occurring ones; but OEP is often not appropriate as models because of the difficulty in further functionalization of the substituents. By contrast, octaphenylporphyrin (OPP) is a suitable β-substituted porphyrin in this respect. Nevertheless, OPP has not been well known owing to difficulties in its synthesis. OPP was first prepared by Friedman,[1] who used the Mannich base approach. The overall yield in the three-step synthesis from 3,4-diphenylpyrrole was below 10%. OPP was also obtained by Treibs and Häberle[2] by heating 3,4-diphenylpyrrole and formaldehyde in acetic acid-pyridine in the presence of HCl. The yield was 20%, but the procedure was tedious. By a modification of the Treibs method, LeGoff and coworkers have prepared several octaalkylporphyrins.[3]

In this paper, we report a simple and high-yield synthesis of octaarylporphyrins from 3,4-diarylpyrroles and formaldehyde. Yields were improved up to 70-80% by DDQ (2,3-dichloro-5,6-dicyanobenzoquinone) oxidation of reaction intermediates identified as octaarylporphyrinogen (OArP'ogen) and octaarylporphodimethene.

3,4-Diphenylpyrrole[1] (2 mmol, 0.42 g) and an excess of 37% formaldehyde (2 ml) were refluxed in ethanol (20 ml). Adding 48% hydrobromic acid (0.5 ml) to the solution gave immediately octaphenylporphyrinogen as a pink-colored precipitate, the structure being confirmed by ^{1}H-NMR spectrum.[4] After refluxing for 1 h, treatment of the reaction mixture with benzene (10 ml) solution of DDQ (3/4 eq, 1.5 mmol, 0.34 g) quickly gave a brown-colored precipitate. After being refluxed for an additional 30 min, the precipitate was collected by filtration and washed successively with methanol-concentrated aqueous ammonia (1:1, v/v),

R = H OPP
R = $CH(CH_3)_2$ O(iPr)PP



methanol, then benzene until the filtrate was colorless. Recrystallization of the precipitate (0.40 g, yield: 90%) from boiling quinoline gave the expected porphyrin as fine purple needles (0.33 g, yield: 72%).[5] As reported by Friedman,[1] OPP is only sparingly soluble in most organic solvents.

To obtain a soluble analogue, we have prepared a p-isopropyl derivative, O(iPr)PP. The procedure was similar to that for OPP. It is found that the reaction of 3,4-di(p-isopropylphenyl)pyrrole[6] leads exclusively to a deep-red solution of octa(p-isopropylphenyl)porphodimethene[7] instead of the porphyrinogen. The initial formation of white precipitates indicates that the porphodimethene is formed by autoxidation of the porphyrinogen.[8] In fact, only 1/4 eq (0.5 mmol) of DDQ was enough to oxidize the reaction intermediate completely to the porphyrin. As expected, O(iPr)PP is soluble in common organic solvents such as chloroform. The product was easily purified by alumina column chromatography (eluent: $CHCl_3$) and by recrystallization ($CHCl_3$-methanol) as fine purple needles (0.53 g, yield: 84%).[9]

The above synthesis is summarized in Chart 1. The first stage is acid-catalyzed cyclization of 3,4-diarylpyrrole with formaldehyde to porphyrinogen. It has been known that normal porphyrinogens are readily oxidized under aerobic conditions.[10] Unexpectedly, OPP'ogen is relatively stable toward autoxidation (path a). Such unusual stability must be attributed to weak electron-donating power and steric crowding of the phenyl substituents. Although some stable porphyrinogens have been reported and characterized, they have substituents at both meso and β-pyrrole positions (hybrid type)[10a,11] or at internal pyrrole nitrogens (N-alkylated type).[11] In the p-isopropyl derivative, the electron-donating power of the substituents is greater than that in OPP'ogen. Initially formed O(iPr)PP'ogen rapidly autoxidizes to porphodimethene (path b). However, further oxidation is limited by steric factors. To our knowledge, only two papers have referred to the isolation of porphodimethenes, which are derived from hybrid-type porphyrins.[10a,12] The stable porphyrinogen and porphodimethene as the intermediates of normally substituted porphyrins have been succesfully isolated for the first time. These two intermediates are interesting compounds in connection with the biosynthesis of protoporphyrin from protoporphyrinogen.

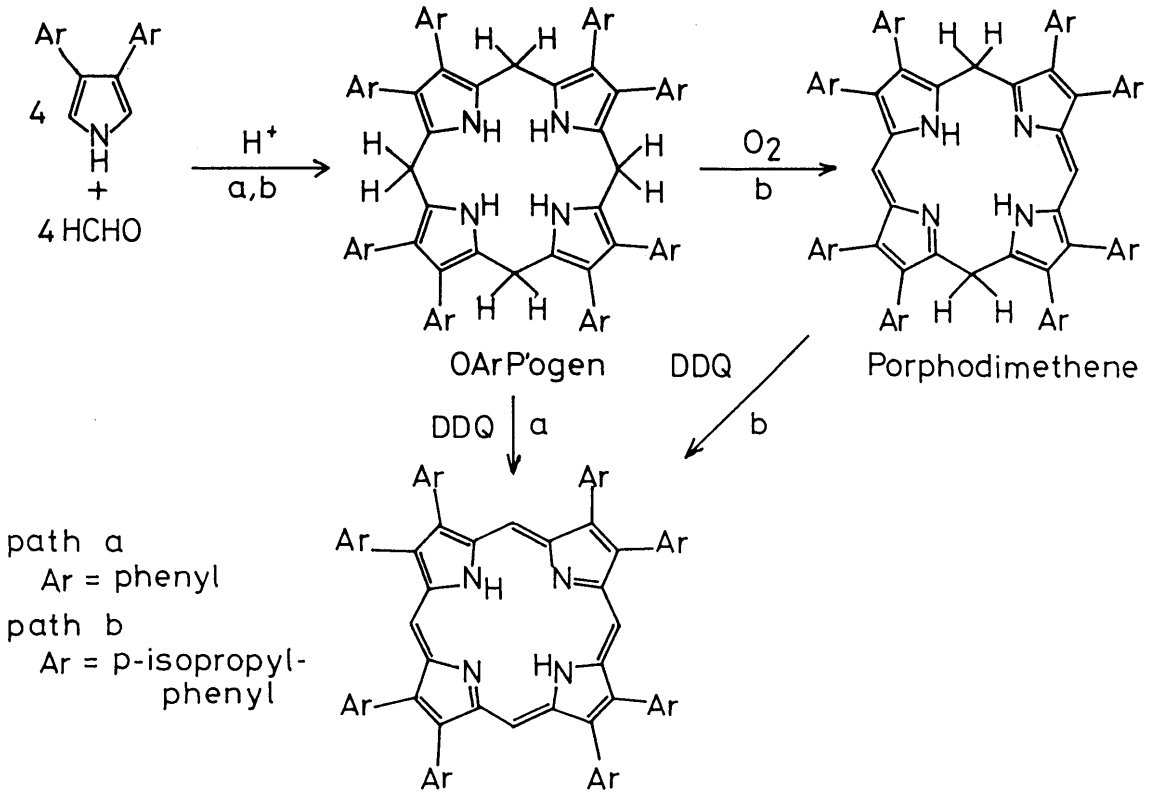


Chart 1

The preparation procedure described here is simple and convenient, and gives octaarylporphyrins in high yields. Furthermore, porphyrinogen or porphodimethenes are easily obtained. Octaarylporphyrins more closely resemble naturally occurring porphyrins. The present high-yield synthesis will allow the preparation of various functionalized OPP analogues.

REFERENCES AND NOTES

1) M. Friedman, J. Org. Chem., 30, 859 (1965).

2) A. Treibs and N. Häberle, Liebigs Ann. Chem., 718, 859 (1968).

3) a) D. O. Cheng and E. LeGoff, Tetrahedron Lett., 1977, 1469; b) K. S. Chamberlin and E. LeGoff, Synth. Commun., 8, 579 (1978); c) idem, Heterocycles, 12, 1567 (1979).

4) The structure of octaphenylporphyrinogen was comfirmed by ^{1}H-NMR spectrum. ^{1}H-NMR ($CDCl_3$) δ 4.08 (s, 8H, meso-H), 7.08-7.24 and 6.8-7.4 (br, internal pyrr NH, and m, Ar-H respectivrly, 44H).

5) UV-vis ($CHCl_3$) λ_{max} 423, 515, 551, 583, 635 nm.

6) Prepared by a method similar to that for 3,4-diphenylpyrrole[1]: ^{1}H-NMR ($CDCl_3$) δ 1.27 (d, J=7.0 Hz, 12H, CH_3), 2.89 (sept, J=7.0 Hz, 2H, -CH<), 6.88 (d, J=2.5 Hz, 2H, pyrr-H), 7.12 and 7.22 (d, J=8.3 Hz, 4H each, Ar-H), 8.23 (br s, 1H, NH).

7) UV-vis ($CHCl_3$) λ_{max} 488 nm (free-base form), and 524 nm (dication form). A small amount of the porphyrin was detected by UV-vis spectrum.

8) We assumed that the initially formed white precipitate was octa(p-isopropylphenyl)porphyrinogen because of the following experimental evidence: (1) The white precipitate was the main product when the reaction was carried out under anaerobic conditions; (2) The white precipitate was converted to porphodimethene in contact with air.

9) UV-vis ($CHCl_3$) λ_{max} (ε, $10^{-3}M^{-1}cm^{-1}$) 422 (241), 516 (20.8), 552 (13.2), 581 (9.9), 635 (4.9) nm; ^{1}H-NMR ($CDCl_3$) δ -3.03 (s, 2H, internal pyrr NH), 1.39 (d, J=7.0 Hz, 48H, CH_3), 3.05 (sept, J=7.0 Hz, 8H, -CH<), 7.39 and 7.92 (d, J=7.9 Hz, 16H each, Ar-H), 10.32 (s, 4H, meso-H).

10) a) D. Dolphin, J. Heterocycl. Chem., 7, 275 (1970); b) H. W. Whitlock and D. H. Buchanan, Tetrahedron Lett., 1969, 3711; c) B. von Maltzan, Angew. Chem. Int. Ed. Engl., 21, 785 (1982).

11) Hybrid type: a) B. Evans, K. M. Smith and J.-H. Fuhrhop, Tetrahedron Lett., 1977, 443; b) H. Ogoshi, H. Sugimoto, T. Nishiguchi, T. Watanabe, Y. Matsuda and Z. Yoshida, Chem. Lett., 1978, 29; c) M. J. Gunter and L. N. Mander, J. Org. Chem., 46, 4792 (1981); d) R. Young and C. K. Chang, J. Am. Chem. Soc., 107, 898 (1985). N-Alkylated type: e) B. Franck and C. Wagner, Angew. Chem. Int. Ed. Engl., 14, 424 (1975); f) R. Timmermann, R. Mattes and B. Franck, ibid., 26, 64 (1987).

12) A series of studies concerning 5,15-dialkyloctaethylporphodimethene have been reported: A. Botulinski, J. M. Buchler, Y. J. Lee and W. R. Scheidt, Inorg. Chem., 27, 927 (1988) and references cited there in.

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