A VERSATILE SYNTHESIS OF TETRABENZPORPHYRINS

David E. Remy

U. S. Army Natick Research and Development Laboratories, Natick, MA 01760
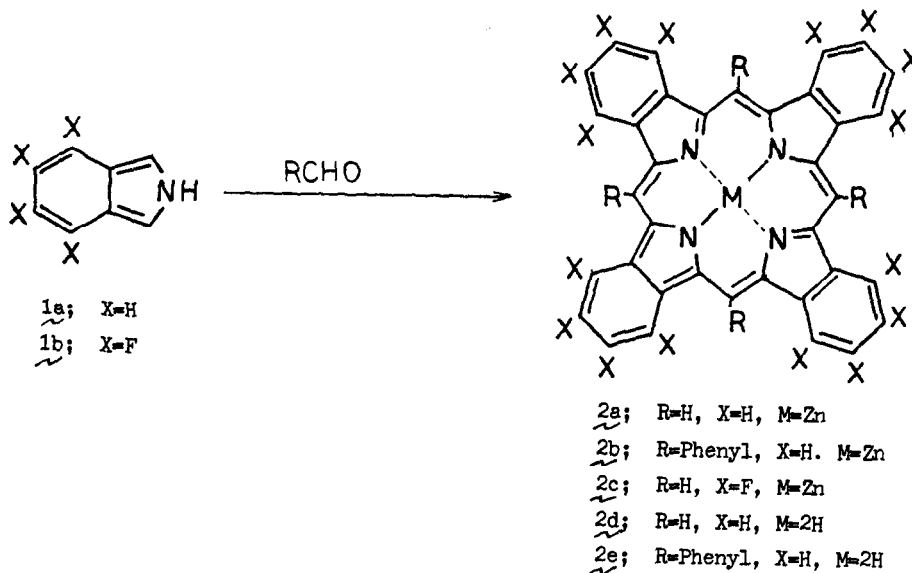
Abstract: The reaction of isoindoles with aldehydes in the presence of metal salts gives the corresponding metallo-tetrabenzporphyrins in excellent yield. The synthesis of zinc tetrabenzporphyrin and its meso-tetraphenyl and hexadecafluoro derivatives is described.

The porphyrins continue to be one of the most extensively investigated classes of substances known. Therefore, it is surprising to find that research on the structurally related tetrabenzporphyrins has progressed relatively slowly despite an ongoing interest in the synthesis and properties of these and related porphyrin-like macrocycles.[1-5] A primary reason for the tardy development of this area has been the lack of effective syntheses for the desired compounds. Previous efforts have been restricted almost exclusively to the preparation and study of the metal-coordinated parent tetrabenzporphyrin, and ring substituted derivatives of this basic macrocyclic system are practically unknown. Aside from a few phthalocyanine-benzporphyrin hybrid structures[6] in which one or more of the porphyrin methine C-H groups have been replaced by nitrogen, very few other variants of the tetrabenzporphyrin structure have been reported.[3,4,17] The present report describes a novel synthesis (SCHEME 1) of the metallo-tetrabenzporphyrin series which relies on the reaction of isoindole (1) with an aldehyde in the presence of a metal ion. The synthesis is remarkably versatile and can be extended to the preparation, in high yield, of a variety of meso-substituted and ring substituted derivatives.

The observation that an unsubstituted isoindole could serve as a monomer for synthesis of the parent tetrabenzporphyrin has been reported.[1,7,8] but the concept was not pursued further nor was consideration given to extending the method to other derivatives. The absence of suitable preparative methods for isoindole coupled with the long-held notion that this precursor would be too reactive for routine use may have inhibited experimentation in this area. Now, recent progress in isoindole chemistry has made several routes available for the preparation and isolation of these reactive heterocycles[7] and the possibility of a synthesis of tetrabenzporphyrins based on isoindole has become extremely attractive. In a structurally, if not mechanistically, analogous fashion this approach resembles the early Rothemund synthesis[9] in which simply porphyrin derivatives were prepared by reaction of pyrrole with an aldehyde. We have adopted an improved Rothemund procedure[10] and use metal salts to assist the reaction of isoindole with an aldehyde and bring about cyclization.

The general procedure is illustrated by the synthesis of zinc tetrabenzporphyrin (2a), which was obtained in 53% yield[11] by reaction of isoindole, monomeric formaldehyde and excess zinc acetate. Isoindole[12] was prepared in essentially quantitative yield by sublimation of 1-2g quantities of 1,2,3,4-tetrahydronaphthalen-1,4-imine through a quartz tube (300mm x 24mm) heated to 600°C at 0.5 mm, and was collected in a liquid nitrogen cooled trap. The trap was allowed to warm to -20°C and 1a was transferred into the reaction flask with cooled degassed

ether under an inert atmosphere. Excess zinc acetate was dissolved in degassed dimethyl-formamide and added to the reaction flask at $0°C$. Monomeric formaldehyde, prepared from para-formaldehyde, was led into the reaction solution with a stream of nitrogen. The temperature was then raised rapidly to drive off the solvent and leave a deep purple solid residue, which was further heated to $375°C$ for 20 minutes. The reaction mixture was then cooled and extracted several times with boiling pyridine. The combined pyridine extracts were reduced in volume and flash chromatographed on silica gel. Successive elution with hexane and tetrahydrofuran/hexane followed by recrystallization from pyridine gave purified 2a. The product and an authentic sample[2] had identical visible and mass spectra. The structure of 2a was further characterized by its NMR spectra: ^{1}H—NMR(TMS, pyridine-d_5) δ 11.28(s,4H,H—C_6),9.80(m,8H,H—C_1), and 8.19 (m,8H,H—C_2); ^{13}C—NMR(TMS, pyridine-d_5) δ 95.3(C_6), 144.8(C_5), 139.6(C_{5a}), 127.3(C_1), and 121.8 (C_2).[13]

SCHEME I

Visible spectra of 2a prepared by us from isoindole and from 2-acetylbenzoic acid[2] show a minor but distinct peak at 460 nm. A similar absorption peak has also been reported for 2a prepared from isoindolinone-3-acetic acid.[1,14] Gouterman[1] attributes the appearance of this band to a porphyrin-like impurity which persisted in the sample even after it had been rigorously purified. The occurrence of this impurity in samples of 2a derived from several different sources is noteworthy and warrants further study.

If formaldehyde is replaced with a different aldehyde in the general reaction procedure, meso-substituted tetrabenzporphyrins are produced. Thus, reaction of benzaldehyde with iso-indole and zinc acetate gave the meso-tetraphenyl derivative 2b in 50% yield after purification

by flash chromatography on silica gel and recrystallization from pyridine: visible spectrum λ max (pyridine) 660 nm (ϵ 38,000), 635(63,000), 595(25,000), 472(220,000), and 446(182,000); ^{1}H-NMR(TMS,CDCl$_3$)δ 8.25(m,8H,H-C$_2$), 7.95(m,12H,H-C$_{3,4}$,), 7.22(m,8H,H-C$_1$), and 7.09(m,8H,H-C$_2$,); ^{13}C-NMR(TMS,DMSO-d$_6$)δ 117.4(C$_6$), 124.7(C$_2$), 125.9(C$_1$), 127.7(C$_4$,), 130.0(C$_3$,), 134.8(C$_2$,), 139.4(C$_{5a}$), 143.6(C$_5$), and 144.1(C$_1$,); mass spectrum 876 (M$^+$).

When isoindole was reacted with formaldehyde or benzaldehyde in the absence of a metal, the free base derivatives 2d and 2e were formed in 4% and 29% yields, respectively. As with the simple porphyrin series, the meso-tetraphenyl derivative 2e was formed in considerably higher yield than the parent 2d. The metal free results contrast sharply to the significantly higher yields (50-53%) obtained when the reactions were carried out in the presence of excess zinc acetate. Clearly, the participation of metal ions in these reactions is an important factor. As a result, we expected the reaction of isoindole with formaldehyde to be greatly assisted by the presence of nickel(II) or copper (II) acetate due to the tendency of these ions to adopt a square planar configuration, which would enable them to perform as template catalysts in the formation of the porphyrin ring. Instead, only trace amounts of the expected products were detected. This result was especially surprising in view of the relatively high yields obtained when these same metals were used in related syntheses.[3,4] Obviously, the role of the metal ion in these reactions has not yet been adequately defined.

A halogenated derivative of the tetrabenzporphyrin system was prepared by reaction of 4,5, 6,7-tetrafluoroisoindole (1b)[15] with monomeric formaldehyde and zinc acetate to give the corresponding zinc hexadecafluorotetrabenzporphyrin (2c) in 57% yield: visible spectrum λ max (CHCl$_3$) 638nm (ϵ 87,000), 580 (21,000), 435 (203,000), and 420 (94,000); mass spectrum 877 (M + 17). Satisfactory ^{1}H, ^{13}C, or ^{19}F NMR spectra could not be obtained for 2c and we speculated that this was due to a paramagnetic species probably present as an impurity associated with the product. This hypothesis was supported by the observation of a broad ESR signal (5 gauss) from the material and the fact that Bonnett[3] experienced a similar problem when he attempted to record the NMR spectra of octamethyltetrabenzporphyrin and several of its metallic derivatives. Cyclic voltammetry exhibited a reversible one-electron reduction wave for 2c at -1.25v (vs. SCE). This reduction potential compares favorably with the value (-1.48v) found for the parent (2a) by Vogeler.[16]

The procedure described in this paper thus provides a potentially general synthesis of the tetrabenzporphyrin series which is simple and results in high yields. The applicability of the synthesis has been demonstrated by the preparation of several tetrabenzporphyrin derivatives. Work is in progress to expand the scope of this reaction and gain information about the reaction mechanism.
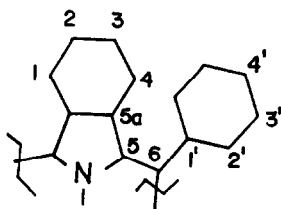
REFERENCES AND NOTES

1. L. Edwards, M. Gouterman, and C. B. Rose, J. Am. Chem. Soc., 98, 7638 (1976).

2. A. Vogler and H. Kunkely, Angew. Chem. Int. Ed. Engl., 17, 760 (1978).

1454

3. C. O. Bender, R. Bonnett and R. G. Smith, *J. Chem. Soc., Perkin Trans. 1*, 771 (1972).

4. D. Dolphin, J. R. Sams and T. B. Tsin, In "Inorganic Syntheses", D. H. Busch, Ed., J. Wiley and Sons, Inc., New York, New York, 1980, Vol. XX, p 155.

5. J. Martinsen, L. J. Pace, T. E. Phillips, B. M. Hoffman, and J. A. Ibers, *J. Am. Chem Soc.*, 104, 83 (1982).

6. J. H. Heilberger, *Justus Liebigs Ann. Chem.*, 529, 205 (1937); J. H. Heilberger and A. von Rebay, *ibid*, 531, 279 (1937); J. H. Heilberger, A. von Rebay, and D. B. Hever, *ibid*, 533, 197 (1938); P. A. Barrett, R. P. Linstead, F. G. Rundal, and G. A. P. Tuey, *J. Chem. Soc.*, 1079 (1940).

7. R. Bonnett and S. A. North, in "Advances in Heterocyclic Chemistry", A. R. Katritzky and A. J. Boulton, Ed., Academic Press, New York, N. Y., 1981, Vol. 29, p 341.

8. R. P. Linstead and E. G. Noble, *J. Chem. Soc.*, 933 (1937).

9. P. Rothemund, *J. Am. Chem. Soc.*, 57, 2010 (1935); *ibid*, 58, 625 (1936); *ibid*, 61, 2912 (1939).

10. R. H. Ball, G. D. Dorough, and M. Calvin, *J. Am. Chem. Soc.*, 68, 2278 (1946).

11. Reported yields of compounds 2a and 2b are based on the isoindole precursor, 1,2,3,4-tetrahydronaphthalen-1,4-imine.

12. J. Bornstein, D. E. Remy, and J. E. Shields, *J. Chem. Soc., Chem. Comm.*, 1149 (1972).

13. Structural assignments for both ^{1}H and [13]C—NMR spectra of 2a and 2b are tentative and are based on the following numbering system in which positions 1, 4 and 2, 3 are considered equivalent:

14. R. P. Linstead and F. T. Weiss, *J. Chem. Soc.*, 2975 (1950).

15. J. Bornstein, D. E. Remy, and J. E. Shields, *Tetrahedron Lett.*, 4247 (1974).

16. A. Vogler, B. Rethwisch, H. Kunkely, J. Hüttermann, and J. O. Besenhard, *Angew. Chem. Int. Ed. Engl.*, 17, 951 (1978).

17. V. N. Kopranenkov, S. N. Dashkevich and E. A. Luk'yanets, *Zh. Obshch. Khim.*, 51, 2513 (1981); *Chem. Abstr.*, 96, 96523d (1982).