

The Preparation and Reactions of Porphyrin *N*-Oxides

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The reaction of octaethylporphyrin with hypofluorous acid and with permaleic acid gives a mono-oxygen adduct formulated as the porphyrin *N*-oxide, a novel chemical system. Octaethylporphyrin *N*-oxide is a sensitive molecule: it is gradually converted into octaethylporphyrin when manipulated under ordinary conditions. Examples of deoxygenation, nucleophilic attack at C-5, and metal complexation are described.

Porphyrin *N*-oxides have not previously been described. We now report two methods, one of common access, for the preparation of a substance which we formulate as octaethylporphyrin *N*-oxide (1), and provide a first account of the chemistry of this delicate system.

Our initial preparation of the *N*-oxide (1) employed hypofluorous acid.¹ This reagent behaves as a source of electrophilic oxygen: benzenoid compounds are converted into phenols,² alkenes give epoxides and/or fluorohydrins,^{3,4} while benzo[*b*]thiophen gives the corresponding sulphone.⁴ *N*-Oxide formation has not previously been encountered with hypofluorous acid, but with octaethylporphyrin (2) it gives an oxygen adduct, which we formulate as the *N*-oxide (1), in a yield of 64%. The same substance can be obtained from the reaction of compound (2) with a number of peracids (peracetic, *m*-chloroperbenzoic, permaleic). In our hands, permaleic acid gave the best yield (spectroscopic, 68%; isolated, 58%) and offers a convenient route to this system.

The evidence on which the formulation (1) is based is as follows. Total elemental analysis accords with a mono-oxygen adduct formula, and this is confirmed by accurate measurement of the molecular ion. The electronic spectrum (Figure 1) is unusual, and shows a broad Soret band at 395 nm (ϵ 106 000) with absorptions in the visible at 528 and 549 nm. This spectrum does not correspond to those of the known products of *meso*-attack [octaethylchlorin (3)]⁵ or of β -attack followed by rearrangement [the isomeric 2-oxochlorin (4)]. Benzylic attack would be expected to give either a 2-(1-hydroxyethyl)porphyrin or its oxidation product, the corresponding 2-acetylporphyrin, which would have visible spectra of the *etio*- and *rhodo*-types, respectively. A 2,3-oxide formulation (5) appears attractive, but such a substance would be expected to have a spectrum of the chlorin type, and to give the oxochlorin under highly acidic conditions.⁶ This behaviour was not observed.

The relatively intense Soret band suggests macrocyclic conjugation (and so militates against 1,2- or 4,5-oxide formulae). Thus, arguing on the basis of visible spectroscopy alone we are forced, by the elimination of plausible alternatives, to the conclusion that the product is the *N*-oxide (1). Other evidence supports this conclusion, but we should make it clear that so far we have not succeeded in obtaining positive physical evidence for the existence of the N–O bond. We have attempted to identify the N–O stretching mode in the i.r. spectrum using the ¹⁸O-derivative. This was unsuccessful: the band at 1 265 cm⁻¹ ascribed to this vibration is broad, and a shift could not be convincingly demonstrated.

The n.m.r. spectrum was in accord with the *N*-oxide formulation. Two singlets (each 2 H) were observed at low field (δ 9.96, 9.78). The signals from one pair of ethyl groups (*i.e.* those on the nitron ring) were appreciably shifted (0.3 p.p.m.) to high field. This is attributed to the deformation of the

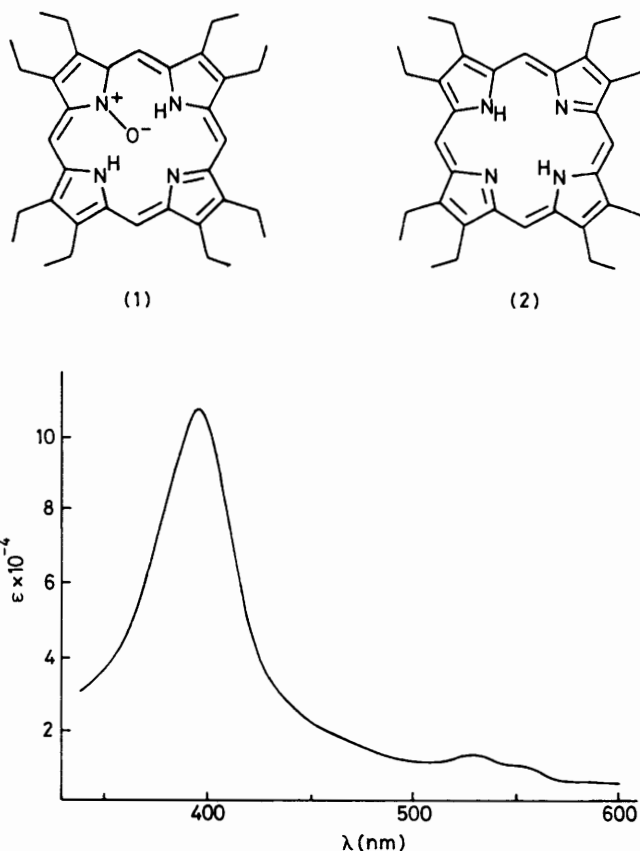


Figure 1. Electronic spectrum of octaethylporphyrin *N*-oxide in chloroform

macrocycle by the *N*-substituent, this being particularly great at the five-membered ring bearing that substituent, so causing a diminution in the deshielding effect experienced by the β -substituents. Analogous effects are observed with *N*-alkyl-⁷ and *N*-amino-⁸ porphyrins.

The *N*-oxide is much less robust than are the *N*-alkyl- and *N*-amino-porphyrins, however. In order to detect the molecular ion in the mass spectrum the injection port must be kept at a temperature (*ca.* 150 °C) which is unusually low in the porphyrin series: on heating, the *N*-oxide gave octaethylporphyrin, and this reaction occurred slowly on silica even at room temperature. Deoxygenation occurred very rapidly with phosphorus trichloride and with phosphorus tribromide. In both cases octaethylporphyrin was the only product detected.

Treatment with base (ammonia or sodium methoxide, in

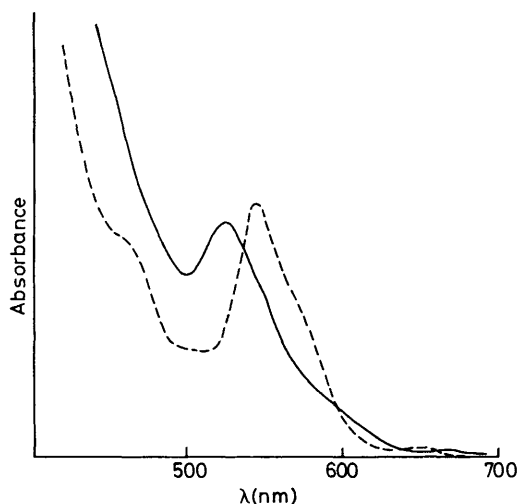
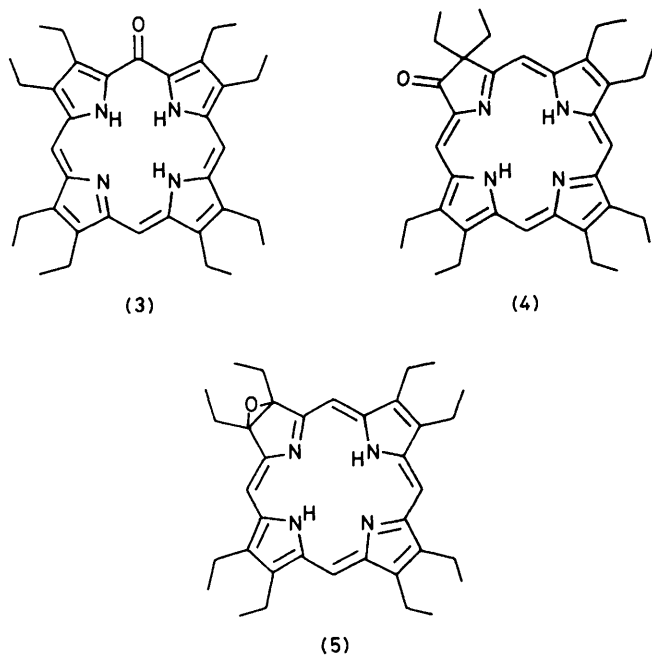
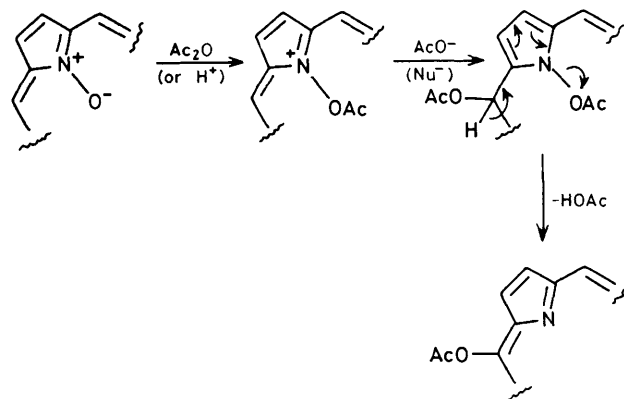


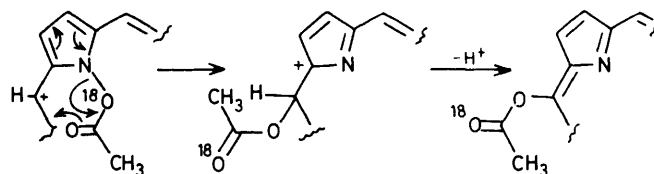
Figure 2. Effect of addition of trifluoroacetic acid on the visible spectrum of octaethylporphyrin *N*-oxide in dichloromethane (— CH_2Cl_2 , - - - $\text{CH}_2\text{Cl}_2 + \text{CF}_3\text{CO}_2\text{H}$)

each case in $\text{CHCl}_3\text{-MeOH}$) had no appreciable effect on the electronic spectrum. However, addition of trifluoroacetic acid caused a shift in the visible band (CHCl_3 , 524 \rightarrow 547 nm) which was reversed when the solution was made basic. A comparison of the relative basicities⁹ of octaethylporphyrin and its *N*-oxide in dichloromethane-trifluoroacetic acid showed that the latter was the more basic. The concentration of trifluoroacetic acid needed for 50% protonation of the *N*-oxide was $1.8 \times 10^{-5} \text{ mol l}^{-1}$, whereas the corresponding value for octaethylporphyrin was $9.9 \times 10^{-5} \text{ mol l}^{-1}$. The curves of $\log [\text{BH}^+][\text{B}]^{-1}$ versus $[\text{CF}_3\text{CO}_2\text{H}]$ were roughly parallel, suggesting (since the porphyrin gave the typical dication spectrum)⁹ that both substances are behaving as diacidic bases. The spectroscopic changes with acidification are shown in Figure 2.

The *N*-oxide (1) reacted with trace amounts of hydrogen chloride in organic solvents to give 5-chloro-octaethylpor-



Scheme 1. (Partial structures)



Scheme 2

phyrin. This was a considerable nuisance, and meant that chlorinated solvents (especially chloroform) had to be washed with aqueous base immediately before an experiment. Treatment of the *N*-oxide (1) with acetic anhydride gave an 87% yield of 5-acetoxyoctaethylporphyrin. This reaction is rationalised as shown in Scheme 1 and is analogous to the reaction of certain pyridine *N*-oxides with acetic anhydride,¹⁰ except that the conditions in the present example are very much milder. There is some evidence for the incursion of an intramolecular reaction as an additional minor pathway: thus, the mass spectrum of the 5-acetoxyporphyrin formed by the reaction of [¹⁸O]octaethylporphyrin *N*-oxide retained about 6% of the label, all of which was in the carbonyl oxygen. Cyclic intramolecular processes (Scheme 2), which accord with this result, have been postulated before, for example in the reaction of acetic anhydride with acridine *N*-oxide.¹¹ However, it appears that the ionic intermolecular pathway shown in Scheme 1 is of major importance, and it is currently under investigation as a general approach to nucleophilic attack at the *meso*-position of porphyrins.

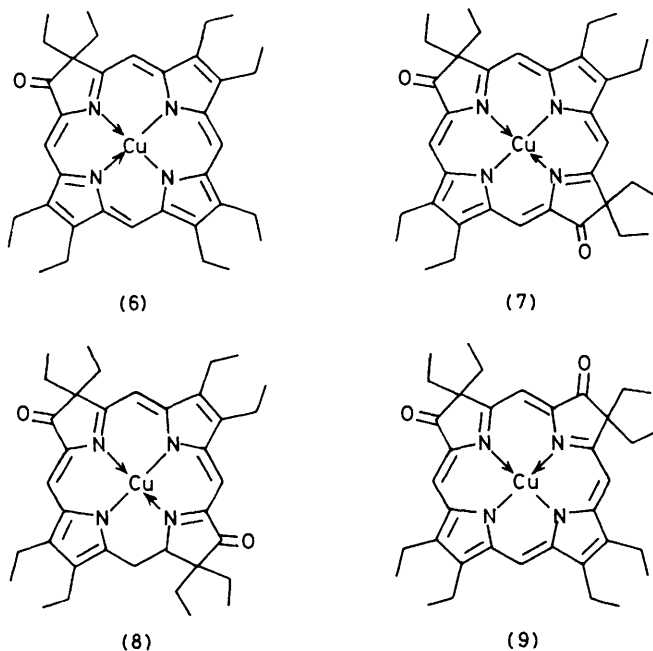
Attempts to make metal complexes of the *N*-oxide (1) have so far generally been frustrated by the ease of formation of the corresponding metalloporphyrins. For example, with zinc(II) acetate in acetic acid-chloroform the *N*-oxide gave a mixture of zinc(II) octaethylporphyrin and zinc(II) 5-acetoxyoctaethylporphyrin (*cf.* Scheme 1). The sole exception was the copper complex, which has been isolated and analysed.

It was thought that this complex might also be obtained directly by treating copper(II) octaethylporphyrin with hypofluorous acid. This proved not to be possible: the reaction gave a complex mixture, the main components of which were products of β -attack (6), (7), (8), and (9).¹²

Experimental

Hypofluorous acid was prepared as described previously² by the reaction of fluorine with ice. Enriched H^{18}OF was prepared from water whose oxygen content was 95 atom-% ¹⁸O.

Thin layer chromatography was carried out on silica unless



otherwise stated. Light petroleum refers to that fraction with b.p. 60–80 °C.

Preparation of Octaethylporphyrin N-Oxide.—(a) *Using hypofluorous acid.* Octaethylporphyrin (150 mg) in chloroform (60 ml, decanted from molecular sieve) was treated at room temperature with hypofluorous acid (ca. 20 mg), delivered in a stream of nitrogen during 5 min. After a further 10 min the solution was shaken vigorously with saturated sodium hydrogen carbonate (6 ml), dried (Na₂SO₄) and evaporated to give a dark solid (135 mg). Analytical t.l.c. (acetone–light petroleum, 1 : 4) showed that this contained minor amounts of starting material (*R_F* 0.80) and 5-chloro-octaethylporphyrin (*R_F* 0.85), a major brown product (the *N*-oxide, *R_F* 0.33) and a minor more polar brown component (*R_F* 0.02). A portion of the crude product (10 mg) was chromatographed on four alumina plates (Merck, aluminium oxide G, Type E, 20 × 20 cm) with acetone–light petroleum (15 : 85). (Working on a larger scale led to smaller recoveries of the *N*-oxide.) The main brown band was extracted with tetrahydrofuran (THF) and rechromatographed on two plates (as before, but with acetone–light petroleum, 1 : 4). The brown band was again extracted with THF: analytical t.l.c. of this extract showed the absence of octaethylporphyrin. The residue after evaporation was dissolved in benzene, filtered, and taken to dryness to give amorphous octaethylporphyrin *N*-oxide (7.3 mg, 64%) as a purple-black solid. Crystallisation was effected, with much loss, from acetone–methanol to give dark microcrystals, m.p. < 250 °C (Found: C, 78.8; H, 8.3; N, 10.35; O, 2.45%; *M*⁺ 550.367. C₃₆H₄₆N₄O requires C, 78.5; H, 8.4; N, 10.2; O, 2.9%; *M* 550.367); λ_{max} (CHCl₃) 395 (ε 106 000) and 528 (8 500), with a shoulder at 549 nm; ν (CsI) 3 500 (br), 1 445, 1 368, 1 265, 1 052, 950 and 830 cm⁻¹; δ (CDCl₃) 9.96 (s, 2 *meso*-H), 9.78 (s, 2 *meso*-H), 4.04 (m, 7-, 8-, 12-, 13-, 17-, 18-CH₂), 3.72 (q, *J* 7.5 Hz, 2-, 3-CH₂), 1.90 (m, 7-, 8-, 12-, 13-, 17-, 18-CH₂Me), and 1.60 (t, *J* 7.5 Hz, 2-, 3-CH₂Me); *m/e* (147 °C) 550 (60), 534 (100), and 519 (5).

A sample of ¹⁸O-enriched octaethylporphyrin *N*-oxide was prepared from isotopically enriched hypofluorous acid as described above, except that the hydrogen carbonate wash was

omitted. Instead the solution was neutralized and dried (Na₂CO₃). The product appeared to lose its isotopic label slowly on standing, and when it was finally used its oxygen content was only ca. 60 atom-% ¹⁸O (Found: *M*⁺ 552.371. C₃₆H₄₆N₄¹⁸O requires *M* 552.371). The i.r. spectrum did not show any clear distinctions from that of the material with natural isotope distribution.

(b) *With various peracids.* Preliminary experiments were carried out to establish suitable conditions for the preparation of octaethylporphyrin *N*-oxide using various peracids. The most promising reactions were scaled up, and the yield of the product was estimated spectroscopically as follows. Peracetic acid (0.12M in CH₂Cl₂, room temperature, 3 h) 39%; *m*-chloroperbenzoic acid (0.02M in CH₂Cl₂, room temperature, 20 min) 26%; permaleic acid (0.14M in CH₂Cl₂, room temperature, 40 min) 68%.

(c) *Using permaleic acid.* A solution of permaleic acid was prepared by adding hydrogen peroxide (30%, 0.3 ml) to a cooled (ice-bath) stirred solution of freshly crushed maleic anhydride (0.6 g) in dichloromethane (acid-free; 30 ml). ['Acid-free' means freshly washed with aqueous NaHCO₃ and dried (Na₂SO₄).] The solution was allowed to come to room temperature and a solution of octaethylporphyrin (25.7 mg) in dichloromethane (acid-free; 20 ml) was added. The mixture was stirred in the dark at room temperature for 40 min. The solution was then washed with aqueous sodium carbonate (2 × 15 ml), the aqueous layers being back-extracted with dichloromethane. The combined organic solutions were washed with distilled water (25 ml), dried (Na₂SO₄), and taken to dryness.

The *N*-oxide was isolated by preparative t.l.c. on silica, eluting with benzene containing 8% (v/v) saturated methanolic ammonia. The polar brown component (*R_F* ca. 0.6; octaethylporphyrin *R_F* ca. 0.8) was eluted with CHCl₃–MeOH (1 : 1), filtered, evaporated to dryness, and crystallised from CH₂Cl₂–MeOH to give dark purple-black prisms (15.4 mg, 58%) of octaethylporphyrin *N*-oxide, identical (t.l.c., i.r., n.m.r.) with the sample prepared above.

Small-scale Reactions of Octaethylporphyrin N-Oxide.—(a) *Heat.* Samples were heated in capillaries at 200 and 250 °C for 30 min. Melting was not observed. T.l.c. showed that, after heating, the first sample contained octaethylporphyrin and the *N*-oxide, the latter predominating; the second sample contained mainly octaethylporphyrin.

(b) *Hydrogen chloride.* Samples were refluxed for 18 h with chloroform and with chloroform containing hydrogen chloride. T.l.c. of the product in both cases revealed the absence of the *N*-oxide, and the presence of octaethylporphyrin (major component) and 5-chloro-octaethylporphyrin (minor component).

(c) *Behaviour of octaethylporphyrin N-oxide on silica.* A solution of octaethylporphyrin *N*-oxide in dichloromethane was applied as a spot to the corner of a square t.l.c. plate. It was eluted in one direction with light petroleum–acetone (85 : 15). After drying in air, the plate was eluted in the second direction. With an interval of 1 h, some decomposition had occurred to give octaethylporphyrin; the amount of decomposition and the number of side reactions increased with the interval between the two elutions. After 72 h some *N*-oxide still remained.

Effect of Acid and Base.—(a) Addition of trifluoroacetic acid to a solution of octaethylporphyrin *N*-oxide in chloroform caused a shift in the visible band (524 → 547 nm). The spectrum did not change after 20 min; addition of an excess of triethylamine regenerated the original spectrum.

(b) The determination of the relative acidities of octaethyl-

porphyrin and octaethylporphyrin *N*-oxide using the method of Rochester and co-workers⁹ showed that the latter was the more basic in CH₂Cl₂-CF₃CO₂H mixtures. The concentration of trifluoroacetic acid needed for 50% protonation of the *N*-oxide was 1.8×10^{-5} mol l⁻¹, compared with a corresponding value for octaethylporphyrin of 9.9×10^{-5} mol l⁻¹.

(c) The electronic spectrum of the *N*-oxide in CHCl₃-MeOH was not affected by addition of ammonia (*d* 0.880), sodium hydroxide, or sodium methoxide.

Reaction with Phosphorus Trichloride.—Octaethylporphyrin *N*-oxide (0.5 mg) was gently warmed (50 °C) with phosphorus trichloride (0.2 ml) and chloroform (0.1 ml) for 5 min. After addition of more chloroform (4 ml) the product was worked up in the normal way. T.l.c. revealed only octaethylporphyrin (spectroscopic yield 61%). The mass spectrum confirmed the presence of octaethylporphyrin and the absence of the 5-chloro-compound.

Reaction with Phosphorus Tribromide.—A solution of octaethylporphyrin *N*-oxide in dichloromethane was treated with a drop of phosphorus tribromide, and the reaction was stirred at room temperature. Samples were removed at intervals and, after suitable treatment (aqueous Na₂CO₃, Na₂CO₃), were examined by t.l.c. After 5 min all of the *N*-oxide had disappeared: octaethylporphyrin was the only product detected.

Reaction with Acetic Anhydride.—An excess of acetic anhydride (1 ml) was added to a stirred solution of octaethylporphyrin *N*-oxide (9.2 mg) in chloroform (10 ml; acid-free) and kept at room temperature (dark; 1.5 h). The solution was washed with aqueous sodium hydroxide (4 × 5 ml) and water, the aqueous layers being back-extracted with chloroform. The combined organic solution was dried (Na₂CO₃) and the products were separated by preparative t.l.c. [benzene containing 8% (v/v) saturated methanolic ammonia]. Two bands were obtained, the least polar of which was identified as octaethylporphyrin. The major red product was eluted from the silica with acetone and recrystallised from chloroform-methanol to give reddish purple prisms (8.6 mg, 87%) of 5-acetoxyoctaethylporphyrin, m.p. 224 °C (lit.,¹³ m.p. 232 °C) (Found: *M*⁺ 592.378. C₃₆H₄₈N₄O₂ requires *M* 592.378); λ_{max.} (CHCl₃) 403 (ε 162 500), 501 (13 900), 533 (6 100), 570 (5 900), and 622 nm (2 000), *m/e* (197 °C) 592 (80%) and 550 (100). The compound was indistinguishable from an authentic sample prepared from octaethylxophlorin and acetic anhydride. On hydrolysis with aqueous sodium hydroxide in the absence of air, octaethylxophlorin was formed.

The ¹⁸O-enriched *N*-oxide was treated with acetic anhydride in the same way, and the product was examined by mass spectrometry. On the basis of the relative intensities of the 592 and 594 ions in the natural and enriched samples, the ¹⁸O-enrichment in the 5-acetoxyoctaethylporphyrin produced in this way was 6%. No ¹⁸O-enrichment was detected in the (*M* - COCH₃) peaks at 550/552.

Preparation of the Copper(II) Complex.—A saturated solution of copper(II) acetate hydrate in methanol (0.5 ml) was added to a stirred solution of octaethylporphyrin *N*-oxide (2.3 mg) in acid-free chloroform (5 ml). After 30 min some unchanged ligand remained. A second portion (0.5 ml) of the methanolic copper(II) acetate was added, and stirring was continued for another 20 min. T.l.c. then showed that no *N*-oxide remained.

The solution was washed with distilled water, dried (Na₂CO₃), and concentrated under reduced pressure. Preparative t.l.c. (CHCl₃-Et₂O, 99 : 1) gave two main bands, the less polar

of which was copper(II) octaethylporphyrin. The copper(II) complex of the β-oxochlorin was not detected. The major, more polar, component was extracted (CHCl₃-MeOH, 1 : 1) and obtained from chloroform-methanol, without heating, as purple crystals (1.3 mg) of copper(II) octaethylporphyrin *N*-oxide (Found: C, 70.35; H, 7.25; N, 9.4%; *M*⁺ 611.281. Calc. for C₃₆H₄₄CuN₄O: C, 70.6; H, 7.25; N, 9.15%; and for C₃₆H₄₄N₄O⁶³Cu: *M* = 611.281); ν (CsI) no peak in 1 600 region; 1 455, 1 260, 1 055, 1 020, and 955 cm⁻¹; *m/e* (227 °C) 611 (45) and 595 (100).

Two dimensional t.l.c. showed that the copper complex decomposed on silica to give copper(II) octaethylporphyrin, together with traces of several other decomposition products. When the copper complex was kept in THF at 45 °C for 1 h, it was essentially all decomposed to give copper(II) octaethylporphyrin and an unidentified yellow compound.

Attempts to make complexes of various other metals have so far been unsuccessful; in some cases the metal complex of octaethylporphyrin is formed. For example zinc(II) octaethylporphyrin was formed when the *N*-oxide was treated with zinc(II) acetylacetonate in methanol or with zinc(II) acetate in methanol. Treatment with zinc(II) acetate in glacial acetic acid-chloroform furnished a mixture of the zinc(II) complexes of octaethylporphyrin and its 5-acetoxy-derivative.

Reaction of Copper(II) Octaethylporphyrin with Hypofluorous Acid.—(With Dr. B. Mateen). A solution of copper(II) octaethylporphyrin (30.4 mg) in chloroform (17 ml) was treated with hypofluorous acid (*ca.* 8 mg) in a stream of nitrogen at room temperature and the colour of the solution changed from red to green; 10 min after the addition was complete, the solution was washed with aqueous sodium carbonate (2 × 20 ml) and water (10 ml) before being dried (Na₂CO₃) and evaporated to dryness under reduced pressure.

T.l.c. (chloroform-light petroleum, 3 : 1) revealed a complex mixture, the main component of which was copper(II) 3,3,7,8,12,13,17,18-octaethyl-2-oxochlorin, prisms (from chloroform-cyclohexane) (5.9 mg, 16%) (Found: *M*⁺ 611.282. Calc. for C₃₆H₄₄N₄O⁶³Cu: *M* 611.281); λ_{max.} (CHCl₃) (absorbance ratios) 377 (28.1), 395sh, 414 (100), 572 (5.6), and 617 nm (24.8), *m/e* (154 °C) 611 (100%), 582 (12), 567 (8), 553 (7), and 538 (4). Three other components were identified (t.l.c., e.s.) by reference to authentic compounds.¹² These were the copper(II) complexes of 3,3,7,8,13,13,17,18-octaethyl-2,3,12,13-tetrahydroporphyrin-2,12-dione (1.6 mg), of 3,3,7,8,12,12,17,18-octaethyl-2,3,12,13-tetrahydroporphyrin-2,13-dione (0.9 mg), and of 3,3,8,8,12,13,17,18-octaethyl-2,3,7,8-tetrahydroporphyrin-2,7-dione (0.6 mg).

Acknowledgements

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