Protiodevinylation: the Schumm Reaction of Vinylporphyrins

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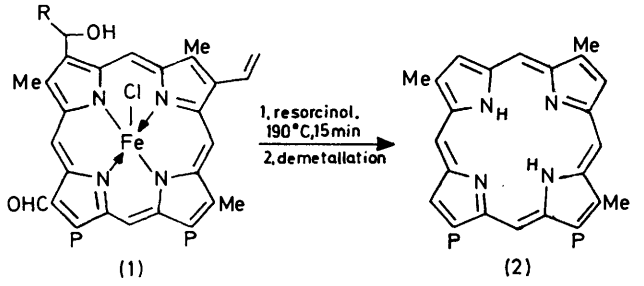
Two intermediates isolated from the protiodevinylation of a vinylporphyrin in molten resorcinol (Schumm reaction) are shown to be 1 :1 adducts. The major pathway in this reaction involves *C*-alkylation of resorcinol.

ALTHOUGH examples of electrophilic devinylation with simple aromatic compounds are rare,[1] this type of reaction has been in routine use in the porphyrin series for nearly 50 years. An important application has been the removal of sensitive side chains (such as vinyl and its relatives) from the porphyrin nucleus in the early stages

[1] Examples exist in the indole series: L. J. Dolby and G. W. Gribble, *Tetrahedron*, 1968, **24**, 6377.

of structural work, a procedure illustrated [2] by the conversion of cytohaemin *a* (1) (from cytochrome *a*) into 18-demethyldeuteroporphyrin (2) (cytodeuteroporphyrin).

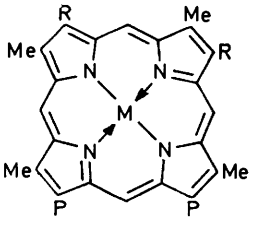


(1) (2)

Kenner and his colleagues have recently made observations on the reaction,[3] but there has been no detailed work on the reaction pathway, which is the subject of this report.

The reaction was discovered by Schumm [4,5] in 1928 during studies on the removal of iron from haemins. He found that heating a mixture of protohaemin (3) and resorcinol at 180 °C led, not to protoporphyrin (4), but to deuterohaemin (5), in which the metal was retained but the two vinyl substituents had been lost. A more detailed study revealed that the fusion conditions caused displacement of α-hydroxyethyl, α-methoxyethyl, hydroxymethyl, and formyl groups at the β-positions of the five-membered rings. As for the reagent, pyrogallol, phloroglucinol, and benzene-1,2,4-triol were found to be effective, whereas catechol, quinol, naphthalene, and camphor were not. The latter two reagents were presumably included to rule out the possibility of a purely thermal reaction in a non-polar and a polar solvent.

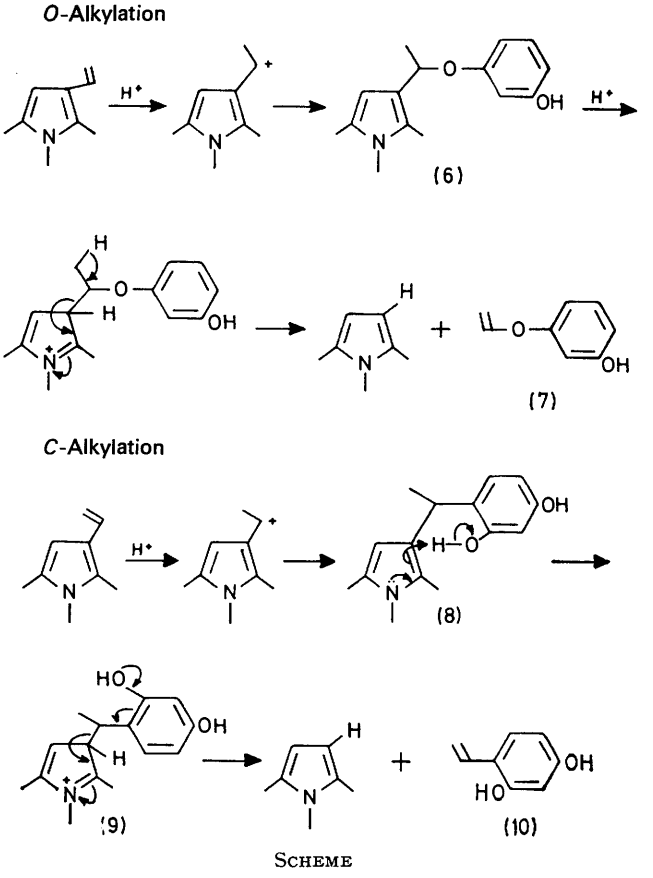
Extending Schumm's preliminary survey, we examined the protiodevinylation of protohaemin, the products being isolated by the concurrent demetallation–esterification procedure described by Grinstein.[6] The reaction with resorcinol did not depend on the presence of oxygen, and acetylene was not detected as a product.



(3) R = CH:CH$_2$, M = FeCl
(4) R = CH:CH$_2$, M = 2H
(5) R = H, M = FeCl

Devinylation of protohaemin was observed with resorcinol, 2-methylresorcinol, 5-methylresorcinol, phloroglucinol, and pyrogallol; but with phenol, 2,4,6-trimethylphenol, 1,3-dimethoxybenzene, 2,4,6-trimethylresorcinol, and 3,5-, 3,4-, and 2,6-xylenols devinylation was not detected, and protoporphyrin dimethyl ester was obtained. Following Schumm's original observation, most reactions of this type have been carried out on the iron(III) complexes. However, the metal is not necessary: [5,7] we found that protoporphyrin itself could be devinylated, as could protoporphyrin dimethyl ester, although in the latter case some starting material was recovered.

The preliminary results show that the 1,3-dihydroxybenzene structural unit is important in the reagent, and two possible reaction types,[8] involving *O*-alkylation or *C*-alkylation by a pseudobenzylic cation, suggest themselves (Scheme). The preliminary evidence favours



SCHEME

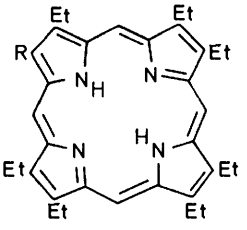
C-alkylation (either 2- or 4-) over *O*-alkylation, since when the appropriate carbon atoms are blocked (in 2,4,6-trimethylresorcinol) reaction does not occur. This, however, could be attributed to a steric effect.

Attempts to isolate the second products in the two proposed processes, that is *m*-hydroxyphenylvinyl ether (7) and 4-(or 2-)vinylresorcinol (10), proved unsuccessful. It seems likely that these products would polymerise

[2] O. Warburg and H. S. Gewitz, *Z. physiol. Chem.*, 1953, **292**, 174; G. S. Marks, D. K. Dougall, E. Bullock, and S. F. McDonald, *J. Amer. Chem. Soc.*, 1960, **82**, 3183.
[3] P. A. Burbidge, G. L. Collier, A. H. Jackson, and G. W. Kenner, *J. Chem. Soc.* (*B*), 1967, 930.
[4] O. Schumm, *Z. physiol. Chem.*, 1928, **176**, 122; **178**, 1.
[5] O. Schumm, *Z. physiol. Chem.*, 1929, **181**, 141.
[6] M. Grinstein, *J. Biol. Chem.*, 1947, **167**, 515.
[7] H. H. Inhoffen, H. Brockmann, and K. M. Bliesener, *Annalen*, 1969, **730**, 173.
[8] A. J. Page, Ph.D. Thesis, London, 1968.

under the reaction conditions. A search was made therefore for the porphyrin intermediate(s) (6) and/or (8). Schumm had originally detected porphyrin intermediates by using electronic spectroscopy.[4] Chu and Chu isolated possible intermediates,[9] but did not identify them, and more recently Kenner and his colleagues [3] isolated a minor fraction from the resorcinol fusion of a divinylhaemin which was regarded, from the ready elimination of resorcinol in the mass spectrometer, as containing a mixture of resorcinol adducts of the *O*-alkylation type (6). Our examination of this reaction with protohaemin,[8] using a lower temperature (130 °C) than that commonly employed, had revealed ten products, two being major ones (isolated yields 7 and 6%). These substances were not crystallised or analysed, but mass and electronic spectra agreed with their formulation as isomeric 3(8)-(1-resorcinylethyl)deuteroporphyrins. The view was taken that they were products of *C*-alkylation,[8] and both gave deuteroporphyrin on fusion with resorcinol at 180 °C.

As the number of intermediate compounds [8,9] demonstrates, protohaemin is too complex a substrate with which to examine the pathway of the Schumm reaction, and we therefore turned to the study of the devinylation of 3,7,8,12,13,17,18-heptaethyl-2-vinylporphyrin (11), as soon as this porphyrin became available.[10] This vinylporphyrin gave heptaethylporphyrin (12) when heated with resorcinol at 180 °C for 1 h. When, however, it was briefly heated (15 min; 180 ⟶ 160 °C) with resorcinol, two new compounds could be isolated. The major product (21%) was obtained crystalline: it had an electronic spectrum of the etio type. The i.r. [$\nu_{max.}$ 3525 cm^{-1} (OH)], n.m.r. [δ 2.25 (d, J 7.5 Hz, 2-CH-CH_3)], and mass spectra [M^+ 642 (0.6%)] agreed with its formu-



(11) R = CH:CH_2
(12) R = H
(13) R = CHMe·O-C$_6$H$_4$-OH
(14) R = CHMe-C$_6$H$_3$(OH)-OH (HO)
(15) R = CHMe-C$_6$H$_3$($OSiMe_3$)-$OSiMe_3$

lation as an adduct between resorcinol and (11), but did not allow us to distinguish with certainty between the product of *O*-alkylation (13) and that of *C*-alkylation (14). This distinction was made by preparing the trimethylsilyl derivative of the adduct under conditions where octaethylporphyrin does not react (*i.e.* attack at nitrogen does not occur) and where resorcinol itself gives a bis-ether. The product was shown by high resolution mass spectrometry to be a bis-trimethylsilyl ether [*e.g.* (15)]. Hence the major adduct is the product of *C*-alkylation: it is regarded as (14) since the 4-position is expected to be more accessible to attack than is C-2. The second product (5%) also behaved as an adduct: because of the very small quantities available it was not obtained crystaline. Fusion with resorcinol at 155 °C caused partial conversion into the other (major) adduct. Although the available evidence does not allow us to distinguish with certainty between the *O*-alkylation and *C*(2)-alkylation formulae for this component the mass spectrum [*m/e* 109 and 549, ascribable to cleavage about the ethereal oxygen of (13); base peak ≡ heptaethylvinylporphyrin] favours the former. Under more vigorous fusion conditions (195—200 °C; 40 min) both adducts gave heptaethylporphyrin (12) as the major product.

It is concluded that the major pathway for the protiodevinylation involves *C*-alkylation. As shown in the Scheme the intermediate (8) can be envisaged both to allow intramolecular protonation of the heteroaromatic nucleus [shown in (8)] and to assist intramolecularly the elimination of vinylresorcinol [shown in (9)]. This type of elimination also occurs readily in the mass spectrometer: heptaethylporphyrin (*m/e* 506) is the base peak in the mass spectrum of (14). The formation of the *C*-alkylation product (14) finds analogy in the reaction of phenol with styrene,[11] and in the reaction of benzyl chloride with resorcinol in the absence of base to give 4-benzylresorcinol as the main product.[12]

EXPERIMENTAL

General experimental conditions and conventions used in presenting data [*e.g.* $\lambda_{max.}$ in nm (ε in parentheses); $\nu_{max.}$ in cm^{-1}] were given previously.[10] Fusion reactions were carried out in a Woods metal bath.

Preliminary Devinylation Experiments with Protoporphyrin Derivatives.—(a) *Survey of reactants and reagents.* The porphyrin (4 mg) and resorcinol (or other reagent) (12 mg) were heated at 185—190 °C for 15 min. The cold product was dissolved in the minimum of pyridine (*ca.* 1 ml) and the solution was diluted with chloroform–methanol (1 : 1; 2 ml). Anhydrous iron(II) sulphate (*ca.* 50 mg) was added, and dry hydrogen chloride was passed to effect demetallation and esterification (Grinstein's method [6]). The solution was poured into ice–water and quickly extracted with chloroform, the organic phase being washed at once with dilute ammonia solution and water. The chloroform solution was dried, concentrated, and chromatographed on alumina with benzene–light petroleum (3 : 1), which separates protoporphyrin dimethyl ester from deuteroporphyrin dimethyl ester. The identity of these products was confirmed by t.l.c. and electronic spectroscopy.

[9] T. C. Chu and E. J. H. Chu, *J. Amer. Chem. Soc.*, 1953, **75**, 3021.

[10] R. Bonnett, P. Cornell, and A. F. McDonagh, *J.C.S. Perkin I*, 1976, 794.

[11] W. Koenigs and R. W. Carl, *Ber.*, 1891, **24**, 3889.

[12] W. J. Hopwood and J. A. Stock, *J. Chem. Soc.*, 1965, 4972.

With protohaemin, the following reagents gave deuteroporphyrin dimethyl ester as the principal product: resorcinol, phloroglucinol, pyrogallol, 2-methylresorcinol, and orcinol. Protoporphyrin dimethyl ester, but not deuteroporphyrin dimethyl ester, was obtained with phenol, 2,4,6-trimethylphenol, 2,4,6-trimethylresorcinol, and 3,4-, 3,5-, and 2,6-xylenol.

With resorcinol the devinylation was successful with protoporphyrin, but protoporphyrin dimethyl ester gave in addition some starting material and an unidentified product.

(b) *Isolation of intermediates with protohaemin.* Protohaemin (100 mg) and resorcinol (470 mg) were mixed and heated at 130 °C for 10 min. The cold product was worked up by Grinstein's method (above). Chromatography on alumina (grade V; alkaline) with methanol–chloroform (1 : 5) gave first a mixture of deuteroporphyrin and protoporphyrin dimethyl esters and a second fraction of more polar components, which were separated by preparative t.l.c. (petroleum–acetone, 85 : 15). Repeated preparative t.l.c. separated ten components, of which two were major. Further purification of these two by t.l.c. gave single porphyrins as red amorphous solids. These are regarded as 3(8)-(1-resorcinylethyl)deuteroporphyrins: isomer 1 (7.1 mg, 7%) softened at 172°; λ 375infl (55 000), 400 (122 000), 498 (10 000), 532 (6 500), 567 (5 100), 591 (1 400), 620 (2 800), and 640 (700); *m/e* 674 (*M*, 60), 659 (5), 565 (*M* − $C_6H_5O_2$, 13), 564 (29), 538 (*M* − $C_8H_8O_2$, 100), and 136 ($C_8H_8O_2$, 170); isomer 2 (6.5 mg, 6%), m.p. 170°; λ 377infl (62 000), 402 (125 000), 501 (10 000), 535 (7 200), 568 (5 300), 593infl (1 500), 622 (2 800), and 642infl (900); *m/e* 674 (*M*, 37), 659 (3), 565 (11), 564 (22), 538 (100), and 136 (63).

Each product, when submitted to the resorcinol melt procedure (a) gave deuteroporphyrin dimethyl ester.

Reactions of 3,7,8,12,13,17,18-*Heptaethyl-2-vinylporphyrin.*—(a) *Devinylation.* Heptaethyl-2-vinylporphyrin [10] (0.8 mg) was mixed with resorcinol (2.7 mg) and kept at 178 ± 2 °C for 1 h. T.l.c. of the product (50% benzene–petroleum) showed that only a trace of 2-vinylheptaethylporphyrin remained. Heptaethylporphyrin, identical with a characterised sample prepared by another route,[13] had been formed, together with some polar material.

(b) *Isolation of intermediates.* Heptaethyl-2-vinylporphyrin (8.3 mg) mixed with resorcinol (26 mg) was heated for 15 min (Woods metal bath; initially 180 °C, cooling spontaneously to 160 °C). Preparative t.l.c. (25% acetone–petroleum) gave three main components, given in order of decreasing mobility; (i) 2-vinylheptaethylporphyrin, λ 504 (1.00), 539 (0.94), 570 (0.55), and 622 (0.31) (extinction ratios given); (ii) adduct I, obtained as a red-brown powder (0.5 mg, 5%) by lyophilisation from benzene (Found: M^+, 642.393. Calc. for $C_{42}H_{50}N_4O_2$: *M*, 642.393), λ 404 (112 000), 505 (9 800), 539 (8 900), 571 (5 300), and 623 (2 700); *m/e* 642 (*M*, 5), 549 (*M* − C_6H_5O, 10), 548 (22), 532 (*M* − $C_6H_6O_2$, 100), 506 (*M* − $C_8H_8O_2$, 26), and 109 ($C_6H_5O_2$, 35); (iii) 2-[1-(2,4-*dihydroxyphenyl*)*ethyl*]*heptaethylporphyrin*, a red-brown powder (2.1 mg, 21%) by lyophilisation from benzene. Repetition of the experiment gave sufficient of the last-named material for crystallisation from chloroform–petroleum, affording red-brown prisms, m.p. 242.5—244.5°; λ 378infl (75 000), 404 (120 000), 503 (11 600), 537 (9 800), 568 (6 350), 594infl (1 400), and 621 (3 600); δ(220 MHz) 10.11, 10.07, 10.03, and 9.90 (s, *meso*-H), 7.86 and 6.60 (m, benzenoid H), 5.55 (m, 2-C*H*·CH_3), 5.45 (s, OH, exchangeable), 4.08 (m, CH_2), 3.75 (m, 3-CH_2·CH_3), 2.25 (d, *J* 7.5, 2-CH·CH_3), 1.88 (m, CH_3), and 1.55 (t, 3-CH_2·CH_3); ν 3 525, 3 320, 1 620, 1 600, 1 520, 950, 837, and 740; *m/e* 642 (*M*, 0.6), 568 (2), 532 (13), 506 (100), 491 [7, *m** 476.5 (506 ⟶ 491), 253 (17), 136 ($C_8H_8O_2$, 4), and 110 (9).

This intermediate (1.5 mg) was treated in pyridine with hexamethyldisilazane and chlorotrimethylsilane. No starting material remained, and no heptaethylvinylporphyrin was detected (t.l.c.). The product, the *bis-o-trimethylsilyl derivative* was more mobile on t.l.c. than the starting material, and was obtained as a red powder on lyophilisation from benzene (Found: M^+, 786.473. $C_{48}H_{66}N_4O_2Si_2$ requires *M*, 786.472); λ 401 (13.9), 500 (1.00), 534 (0.78), 567 (0.50), and 619 (0.35) (extinction ratios given) *m/e* 786 (*M*, 2), 714 (*M* − $SiMe_3$ + H, 2), 642 (0.5), 534 (23), 532 (40), and 506 (100).

Octaethylporphyrin was not trimethylsilylated under the same conditions.

(c) *Pyrolysis of intermediates.* In small-scale experiments the two intermediate compounds from the foregoing experiment were heated in capillaries, either alone or mixed with an approximately five-fold excess of resorcinol, and the products were examined by t.l.c. When heated alone at 165 °C for 15 min, neither compound was changed. After the minor intermediate (adduct I) had been heated with resorcinol at 155 °C for 15 min it was recovered together with a minor amount of the other intermediate (mixed t.l.c.). The major intermediate was recovered after heating under these conditions, but under more vigorous conditions (195—200 °C; 40 min) heptaethylporphyrin was the major product.

We are grateful to Shell Research Ltd. and to the Drapers Company for financial support.

[6/1157 *Received*, 17*th June*, 1976]

[13] I. H. Campion-Smith, Ph.D. Thesis, London, 1973.