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# POLYFORMYLATION OF COPPER(II) PORPHYRINS

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*Vilsmeier formylation of copper(II) octaethylporphyrin (1) is shown to yield the copper(II) complexes of meso-monoformyloctaethylporphyrin, meso-α,β- and meso-α,γ-diformyloctaethylporphyrins, meso-α,β,γ-triformyloctaethylporphyrin, and meso-α,β,γ,δ-tetraformyloctaethylporphyrin. There is therefore no difference in regioselectivity of meso-diformylation between the octaethylporphyrin and etioporphyrin-I series.*

Though an established theory of substituent effects in electrophilic substitution of benzenoid compounds exists, the situation with regard to substituent orientation in electrophilic poly-substitution of porphyrin systems remains confused. Nitration of octaethylporphyrin gives[1] a mixture of α,β- and α,γ-dinitro-octaethylporphyrins, but chlorination affords[2] only the α,γ-dichloro derivative. Nitration of α-nitroporphin, however, gives[3] α,β-dinitroporphin as the only disubstituted product. It has been reported that nitration of zinc(II) octaethylporphyrin [with $Zn(NO_3)_2.6H_2O$ in acetic anhydride] produces[4] only α,γ-dinitro-octaethylporphyrin, and also that Vilsmeier formylation (with $POCl_3$/DMF) of copper(II) octaethylporphyrin (1) gives the α,γ-diformyl derivative as the only disubstituted product. This last conclusion has been confirmed by Ponomarev et al.,[5] though the unique production of only the α,γ-disubstituted product was interpreted as being due to steric rather than the electronic factors favored by Watanabe et al.[4]

The situation is yet more confusing when one considers that Vilsmeier formylation of cobalt(II) etioporphyrin-I (2) yields[6] both the α,β- and α,γ-disubstituted products, and this observation has recently been confirmed by Ponomarev et al.,[7] who also isolated the α,β,γ-triformyl compound. In the present Letter we show that explanations[4,5,7] put forward to rationalize the differences between diformylation in the octaethylporphyrin and etioporphyrin-I series are unnecessary since the α,β- and α,γ-diformylporphyrins are indeed formed in each case.

Prolonged treatment (18 hours) of copper(II) etioporphyrin-I (3) with excess Vilsmeier reagent at 50°C in 1,2-dichloroethane, followed by hydrolysis and aqueous work-up, and then separation on preparative thick layer plates (silica gel, elution with toluene), gave four major bands. The compounds isolated from this separation were identified,[8] in order of increasing polarity, as copper(II) α,γ-diformyletioporphyrin-I (4) (13%), copper(II) α,β-diformyletioporphyrin-I (5) (16%), copper(II) α,β,γ-triformyletioporphyrin-I (6) (16%), and copper(II) α,β,γ,δ-tetraformyletioporphyrin-I (7) (<1%).[9] These compounds, with the exception of (7), were demetalated in 1:1 $H_2SO_4/CF_3CO_2H$ to give the appropriate metal-free derivatives (8) → (10) which also were fully characterized.

Similar treatment of copper(II) octaethylporphyrin (1) with excess Vilsmeier reagent at 80° in 1,2-dichloroethane for 3 hours[10] gave a mixture of formylated products which were initially separated on silica gel by column chromatography (elution with toluene) to afford copper(II) α-formyloctaethylporphyrin (11)[8,11] (20%), copper(II) diformyloctaethylporphyrin (23%), copper(II) α,β,γ-triformyloctaethylporphyrin (12) (9%), and copper(II) α,β,γ,δ-tetraformyloctaethylporphyrin (13) (<1%).[9] Further examination of the diformylated fraction by high pressure liquid chromatography (HPLC)[12] showed this material to be an almost 1:1 mixture of two isomers (Figure 1) (assuming equal extinction coefficients at 405 nm). These isomers were separated by careful preparative TLC on silica gel (elution with toluene), to give the copper(II) α,β- and α,γ-diformyl compounds (14) (10%) and (15) (11%), respectively, with the α,γ-isomer (15) being the least polar of the two. Compounds (14) and (15) were also fully characterized.

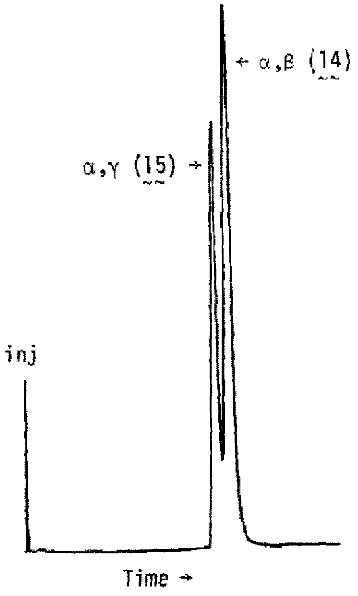
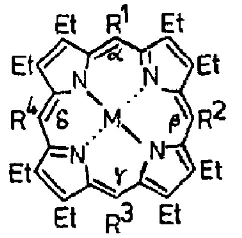


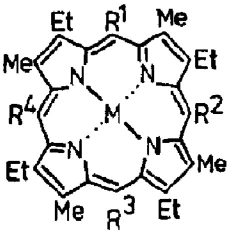
*FIGURE 1: HPLC[12] of the diformyloctaethylporphyrin copper(II) complexes.*

The copper(II) complexes (11), (12), (14), (15) were demetalated using 1:1 $H_2SO_4/CF_3CO_2H$, and were further characterized, particularly by NMR spectroscopy at 360 MHz. The α,β- and α,γ-diformyloctaethylporphyrins (16) and (17), respectively, showed very characteristic NMR spectra which are shown, in part, in Figure 2. As would b expected,[13] the α,β-isomer (16) (Figure 2A) shows four separate methylene signals, while the α,γ isomer (17) (Figure 2B) exhibits two equal intensity quartets. The identity of isomer (16) was further confirmed by comparison with authentic α,β-diformyloctaethylporphyrin obtained[14] by Vilsmeier formylation of copper(II) trans-octaethylchlorin [to give[15] copper(II) γ,δ-diformyl-trans-octaethylchlorin], followed by demetalation and oxidation to the porphyrin state.

We therefore conclude that formylation of copper(II) octaethylporphyrin gives both of the possible diformylation products. These conclusions are contradictory to those of Watanabe et al.[4] and Ponomarev et al.[5] for the octaethylporphyrin series. Previous evidence[4,5] for unique formation of only the α,γ-diformyl product (17) rests solely on symmetry observed in the NMR spectrum. In the spectrum published by Watanabe et al.[4] we can discern a small resonance to high field of the two methylene resonances which we attribute to a minor amount of the α,β-isomer (16) (Figure 2). Moreover, the relative integrations of the methylenes appear[4] not to be 1:1, and neither do the peaks appear as pure quartets (cf. Figure 2B). At the present time we cannot say



(1) M = Cu; $R^{1-4}$ = H
(11) M = Cu; $R^1$ = CHO; $R^{2-4}$ = H
(12) M = Cu; $R^{1-3}$ = CHO; $R^4$ = H
(13) M = Cu; $R^{1-4}$ = CHO
(14) M = Cu; $R^{1,2}$ = CHO; $R^{3,4}$ = H
(15) M = Cu; $R^{1,3}$ = CHO; $R^{2,4}$ = H
(16) M = 2H; $R^{1,2}$ = CHO; $R^{3,4}$ = H
(17) M = 2H; $R^{1,3}$ = CHO; $R^{2,4}$ = H



(2) M = Co; $R^{1-4}$ = H
(3) M = Cu; $R^{1-4}$ = H
(4) M = Cu; $R^{1,3}$ = CHO; $R^{2,4}$ = H
(5) M = Cu; $R^{1,2}$ = CHO; $R^{3,4}$ = H
(6) M = Cu; $R^{1-3}$ = CHO; $R^4$ = H
(7) M = Cu; $R^{1-4}$ = CHO
(8) M = 2H; $R^{1,3}$ = CHO; $R^{2,4}$ = H
(9) M = 2H; $R^{1,2}$ = CHO; $R^{3,4}$ = H
(10) M = 2H; $R^{1-3}$ = CHO; R = H

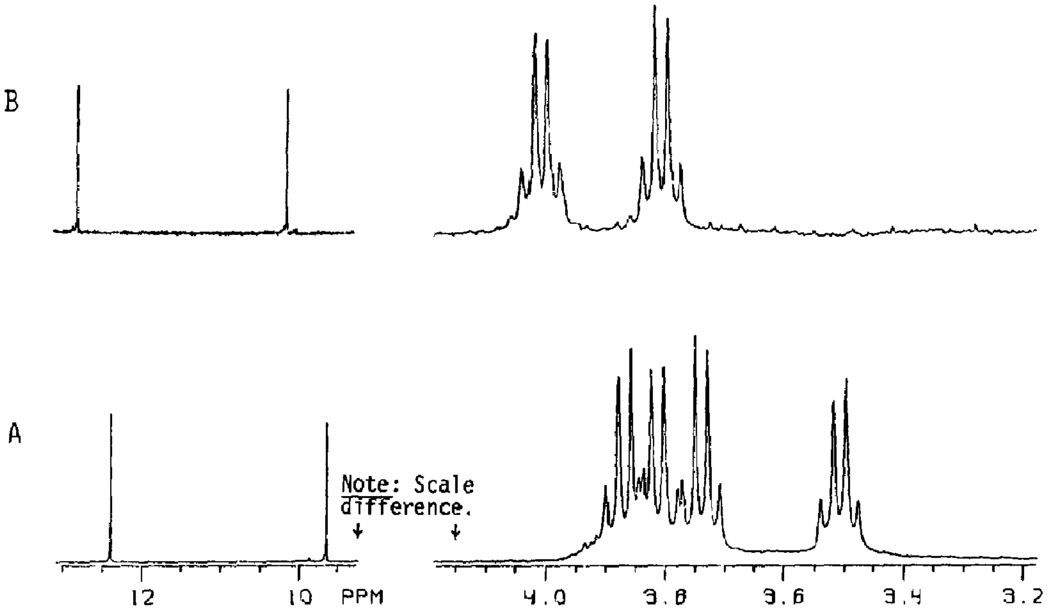


*FIGURE 2: 360 MHz NMR spectra, in $CDCl_3$, of the formyl, meso, and methylene regions in:* A, α,β-*Diformyloctaethylporphyrin (16), and* B, α,γ-*Diformyloctaethylporphyrin (17).*

whether the previous workers preferentially crystallized the more symmetrical, presumably less soluble, α,γ-diformyl isomer (**17**), or whether the symmetry in the NMR spectrum is due to aggregation effects.[16] Another possibility could be that deformylation takes place in 100% $H_2SO_4$[4,5] (but not in 1:1 $H_2SO_4/CF_3CO_2H$), and that the α,β-isomer deformylates faster than α,γ. A critical study of all these possibilities is underway.

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8. All compounds were identified by combustion analysis, mass and electronic spectroscopy, NMR spectroscopy (when diamagnetic), and comparison with authentic samples or literature data, when applicable.
9. On account of the small amounts available, this compound was identified only by mass spectrc scopy.
10. When this reaction was run under precisely the conditions described by Watanabe et al.[4] the products obtained were (**11**) (28%), (**14**) (18%), and (**15**) (18%).
11. Isolation of monoformylated material here is in agreement with the conclusions of Ponomarev et al. (Refs. 5, 7) that octaethylporphyrin, for steric reasons, is less reactive toward the Vilsmeier reagent at the meso positions than is etioporphyrin-I.
12. A Waters Associates ALC/GPC 201 was used with a UV detector set at 405 nm. One E. Merck Hibar II LiChrosorb Si60 column (5μ; 250 mm x 4.6 mm ID) was eluted with 0.2% methanol in methylene chloride at 2 mL/min, which created a back-pressure of approx. 2000 psi.
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16. α,β-Dinitro-octaethylporphyrin derivatives self-aggregate strongly, whereas the α,γ-isomers do not: R.J. Abraham, B. Evans, and K.M. Smith, Tetrahedron, 34, 1213 (1978); M. Chikira, H. Kon, R.A. Hawley, and K.M. Smith, J.C.S. Dalton Trans., 245 (1979). However, in a mixtui of diformylated compounds, it might be expected that the α,β-isomer would self-aggregate anc also would aggregate with the α,γ-isomer, thereby averaging the chemical shifts to a certair extent. An NMR aggregation study is underway.

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