Steric control of tautomerism in tetrapyrroles: iso-oxophlorins

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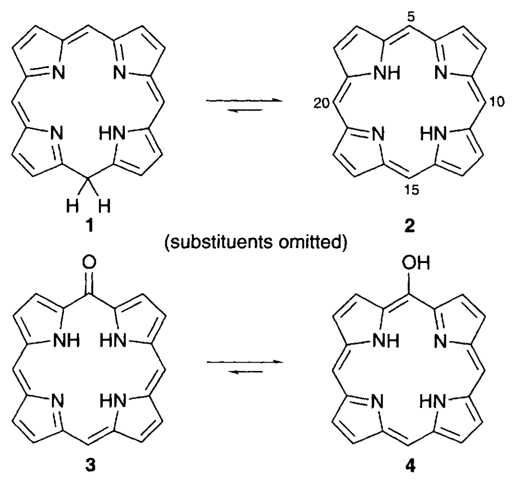
5-Oxophlorins possessing a 15-substituent (*e.g.* 5) tend to exist in the tautomeric iso-oxophlorin form 8 in order to minimize steric interactions between the 15-group and its abutting substituents; the structure of 8 is established by spectroscopic methods and by X-ray crystallography.

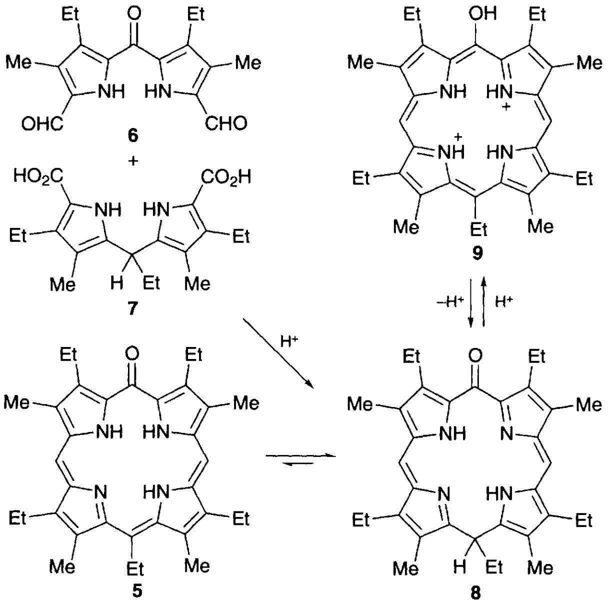
Isoporphyrins **1** are tautomers of porphyrins **2** in which a hydrogen is transferred to a meso-carbon from its normal position on a nitrogen atom.[1,2] Except in unusual circumstances (such as when a meso-carbon is geminally substituted)[1–3] isoporphyrins are very unstable with respect to transformations back to the fully conjugated porphyrin chromophore. Oxophlorins are very interesting tetrapyrrole macrocycles which possess a carbonyl group at a meso-carbon and exist in the keto-form **3** rather than enol-form **4** in neutral solution.

In acidic solution or in the presence of divalent metals, the enol-structure predominates; with trivalent metals such as iron(III), either the keto- or enol-form can predominate, depending upon the pH.[4] Here we show that the introduction of steric congestion at a meso-position in oxophlorins can cause the iso-oxophlorin tautomer to predominate both in the solid state and in solution. Several approaches have been developed for the synthesis of oxophlorins,[5] but syntheses of meso-substituted oxophlorins are scarce in the literature. A number of syntheses of meso-substituted oxophlorins *via* oxygenation of meso-substituted metalloporphyrins have been published,[6] but there have been no other studies described since. Oxophlorins can readily be prepared directly *via* a MacDonald-type (*i.e.* '2+2') condensation involving the coupling of 1,9-diformyldipyrroketones with dipyrromethane-1,9-dicarboxylic acids;[7] we used this approach in the present work.

Preparation of the 15-ethyl-5-oxophlorin **5** was accomplished *via* condensation of the 1,9-diformyldipyrroketone[8] **6** and the 5-ethyldipyrromethane-1,9-dicarboxylic acid **7**.[9] Under the acidic conditions of the reaction, both the mono- and di-cations of the oxophlorin **5** were observed spectrophotometrically. Basic work-up of the reaction product afforded predominantly the novel compound **8** possessing an unusual optical spectrum (Fig. 1) and a proton NMR spectrum which featured characteristic peaks (in $CDCl_3$ at δ 12.65 exchangeable 2NH; 6.91 10,20-H; 4.10 15-H triplet; 1.97 15-CH_2CH_3 multiplet; 0.85 15-CH_2CH_3 triplet). The molecular structure of **8** was further confirmed by X-ray crystallography (Fig. 2).‡ The macrocycle exhibits a slightly ruffled conformation with a mean deviation of 0.141 Å for the 24 core atoms from their least-squares plane.



(substituents omitted)



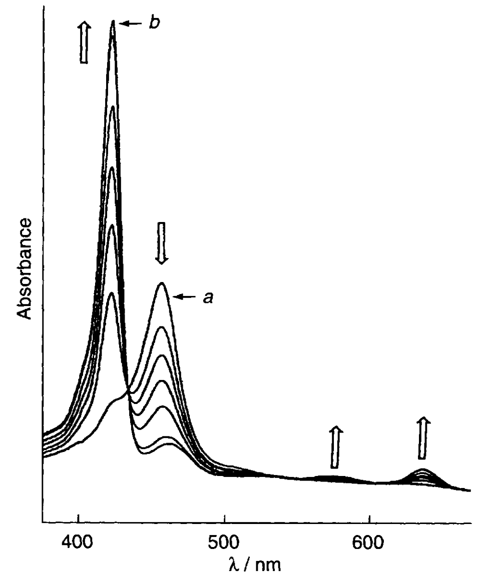


Fig. 1 Optical spectra (in $CHCl_3$) of iso-oxophlorin **5** (*a*) and the oxophlorin dication **9** (*b*), and a demonstration of the conversion of **5** into **9** upon treatment with TFA (isobestic points: 433, 544 and 606 nm). The conversion of **9** into **5** can also be demonstrated, with isosbestic points (not shown), by addition of NEt_3 to **9** in CH_2Cl_2.

The C-15 ethyl group curls back over the macrocycle. The C=O bond length is 1.236(2) Å, in good agreement with expected C=O bond lengths. By comparison with the isoporphyrin–porphyrin equilibrium, the structure **8** can be described as an iso-oxophlorin which is remarkably stable with regard to its 'aromatic' oxophlorin tautomer **5**. Given the opportunity to become a fully conjugated hydroxyporphyrin (for example by protonation–Fig. 1) the chromophore converts reversibly between oxophlorin dication **9** and iso-oxophlorin, depending upon pH. We propose that the novel iso-oxophlorin tautomer predominates under non-acidic conditions because the presence of an sp^3 carbon at position 15 allows steric strain to be relieved; the further obvious extrapolation is that the gain in aromatic stabilization by having the fully conjugated oxophlorin form **5** is not sufficient to favour that tautomer when one takes into account the steric congestion introduced in **5** between the abutting 13,17-substituents and the 15-ethyl by the presence of the sp^2 carbon at the meso-position. In contrast, the aromatic stabilization afforded by formation of the conjugated porphyrin chromophore, as in dication **9** or in the 5-acetoxy-15-ethylporphyrin **10** is clearly sufficient to outweigh the steric strain introduced at the 15-sp^2 carbon in these compounds. 5-Acetoxy-3,7,12,15,18-pentaethyl-2,8,13,17-tetramethylporphyrin was obtained from **8** by treatment with acetic anhydride in pyridine[4] and showed the expected peaks in its proton NMR spectrum (in $CDCl_3$ at δ 10.12 10,20-H; 2.89 meso-OCO*Me*; −2.48, −2.55 2NH) and a characteristic phyllo-type[11] porphyrin optical spectrum.

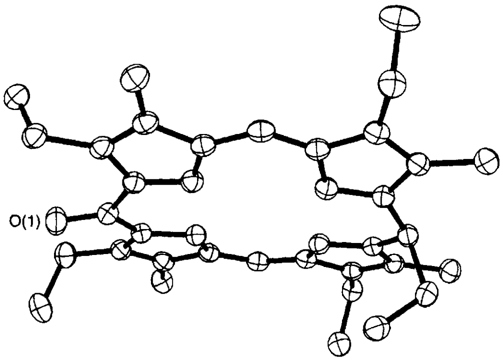
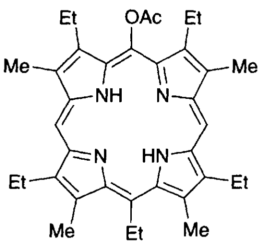


Fig. 2 Molecular structure‡ of iso-oxophlorin **8**



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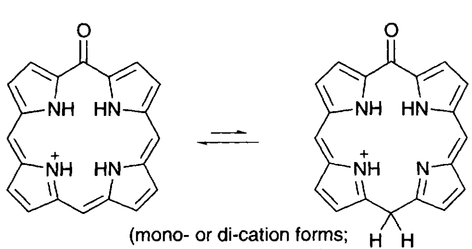

(mono- or di-cation forms; substituents omitted)

11 **12**

Finally, it should be mentioned that the transient existence of 15-iso-5-oxophlorins has been postulated in the literature. An equilibrium between **10** and **11** was postulated in 1968[4] to explain the quite unexpected and completely regiospecific 15-deuteriation of 5-oxophlorins under acidic conditions in the presence of deuteriated solvents. Species **11** was only transiently apparent (but not directly observed) presumably because it does not possess the steric encumbrance that oxophlorin **5** must accommodate, and which it does so by the preponderance of the unconjugated structure **8** in the tautomeric equilibrium.

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Footnotes

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‡ Crystals of **8** were grown from a mixture of methanol, tetrahydrofuran and water. A prismatic single crystal was selected with dimensions 0.40 × 0.34 × 0.14 mm. The unit cell was triclinic $P\bar{1}$ with cell dimensions a = 11.1398(6), b = 12.0341(6), c = 12.6777(7) Å, α = 64.339(4), β = 79.556(4), γ = 71.772(4), V = 1452.96(13), Z = 2 (FW = 522.72, ρ_{calc} = 1.057 g cm^{-3}, μ = 0.562 mm^{-1}). X-Ray diffraction data were collected on a Siemens P4 diffractometer with a rotating anode [λ(Cu-Kα) = 1.54178 Å] at 130(2) K in $\theta/2\theta$ scan mode to $2\theta_{max}$ = 112°. Of 7611 reflections measured ($\pm h$, $\pm k$, $\pm l$) 3800 were independent and 3577 had $I > 2\sigma$ (R_{int} = 0.0189). The structure was solved by direct methods and refined (based on F^2 using all independent data) by full-matrix least-squares methods (Siemens SHELXTL V. 5.02); number of parameters = 359. Hydrogen atom positions were located by their idealized geometry and refined using a riding model. A difference map followed by subsequent refinement revealed that two of the methyl groups bear statistical sets of hydrogens rotated by approximately 60° relative to each other. Core hydrogens were present at 50 percent occupancy for each nitrogen. An absorption correction was applied using XABS2.[10] Final R factors were $R1$ = 0.0326 (based on observed data) and $wR2$ = 0.0806 (based on all data); the maximum residual electron density was 0.175 e Å^{-3}. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/50.

References

1 R. B. Woodward, *Pure Appl. Chem.*, 1961, **2**, 383; *Ind. Chim. Belge.*, 1962, **27**, 1293.
2 D. Dolphin, R. H. Felton, D. C. Borg and J. Fajer, *J. Am. Chem. Soc.*, 1970, 92, 743.
3 E. G. H. Xie and K. M. Smith, *Tetrahedron Lett.*, 1992, **33**, 1197; K. M. Barkigia, M. W. Renner, H. Xie, K. M. Smith and J. Fajer, *J. Am. Chem. Soc.*, 1993, **115**, 7894; S. Gentemann, S. H. Leung, K. M. Smith, J. Fajer and D. Holten, *J. Phys. Chem.*, 1995, **99**, 4330.
4 A. H. Jackson, G. W. Kenner and K. M. Smith, *J. Chem. Soc. (C)*, 1968, 302.
5 K. M. Smith, in *Porphyrins and Metalloporphyrins*, ed. K. M. Smith, Elsevier, Amsterdam, 1975, pp. 36, 40–41, 630 and references cited therein; R. Bonnett, M. J. Dimsdale and G. F. Stephenson, *J. Chem. Soc. (C)*, 1969, 564; G. H. Barnett, M. F. Hudson, S. W. McCombie and K. M. Smith, *J. Chem. Soc., Perkin Trans. 1*, 1973, 691.
6 G. H. Barnett, B. Evans and K. M. Smith, *Tetrahedron* 1975, **31**, 2711; B. Evans and K. M. Smith, *Tetrahedron*, 1977, **33**, 629.
7 P. S. Clezy, A. J. Liepa and G. A. Smythe, *Aust. J. Chem.*, 1970, **23**, 603.
8 P. S. Clezy, A. J. Liepa, A. W. Nichol and G. A. Smythe, *Aust. J. Chem.*, 1970, **23**, 589.
9 D. A. Lee, J. M. Brisson and K. M. Smith, *Heterocycles*, 1995, **40**, 131.
10 S. R. Parkin, B. Moezzi and H. Hope, *J. Appl. Cryst.*, 1995, **28**, 53.
11 K. M. Smith, in *Porphyrins and Metalloporphyrins*, ed. K. M. Smith, Elsevier, Amsterdam, 1975, p. 23.

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