Stabilization of neutral oxophlorin π-radicals by bulky meso-alkyl groups

Richard G. Khoury,[a] Laurent Jaquinod,[a] Amy M. Shachter,[b] Nora Y. Nelson[a] and Kevin M. Smith*[a]†

[a] *Department of Chemistry, University of California, Davis, CA 95616, USA*
[b] *Department of Chemistry, Santa Clara University, Santa Clara, CA 95053, USA*

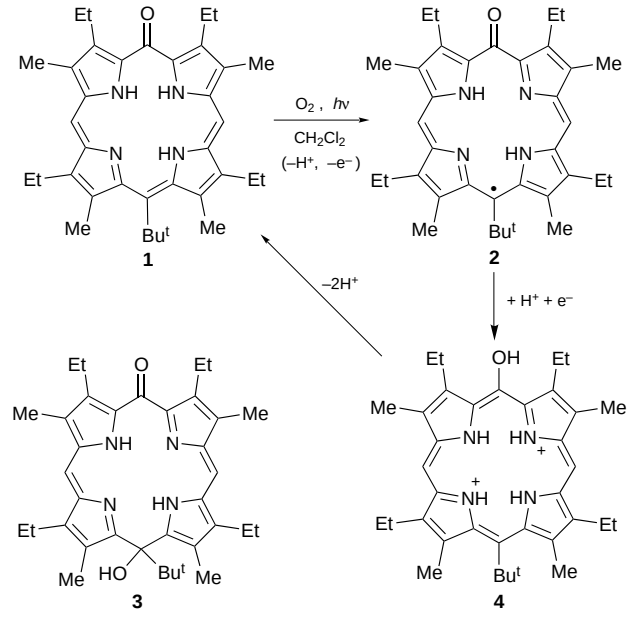
The 15-*tert*-butyl-5-oxophlorin 1 forms a stable, neutral π-radical species 2, in high yield; the 13,17-bis-unsubstituted 5-oxophlorin analogue 5, under similar conditions, affords the 15-iso-5-oxophlorin 6 and 15-hydroxy compound 7 (both characterized by X-ray crystallography), the latter demonstrating the trapping of the π-radical by dioxygen.

The syntheses and chemistry of tetrapyrrole π-free-radicals is one of the few fields of porphyrin chemistry which remains relatively undeveloped. It is also a fact that the preparation of other stable and useful π-radicals are found only infrequently in the literature. Published work on π-radicals has focused on the study of their electronic structure,[1] their use to create charge transfer species in molecular conductors,[2] their use in synthesis[3] and their involvement in biological systems.[4] Compounds such as quinones and related compounds play important roles as mediators in some electron-transfer processes which occur in mitochondria and in chloroplasts. Radicals also react with transition metal ions that have appropriate reduction potentials.[4] In biological systems, haemes in haemoglobin and myoglobin are degraded to bile pigments *via* a key intermediate, suspected to be a meso-oxyporphyrin π-neutral radical or an oxophlorin radical species reacting quickly with O_2.[4,5] In 1975, studies by Fuhrhop and co-workers showed that oxophlorins and their metal complexes are oxidized at low potentials yielding fairly unstable neutral π-radicals which underwent a variety of secondary reactions to generate, for instance, 5,15-dioxoporpho-10,20-dimethenes.[6] Examples of radical dimerizations of oxophlorins at the 15-positions[6] led us to believe that the meso-15-position has unique chemical reactivity.[5] We showed that electronic and steric features at the 15-position enable one to exert control over the oxidation potential of the oxophlorin, and direct a novel dimerization process to the 10-position, a phenomenon which has been used for the reversible self-assembly of a cyclic tetra-oxophlorin.[7] In order to further investigate the chemical properties associated with 15-meso-substituents, we targeted 15-*tert*-butyl-5-oxophlorins in the hope that radical formation and stabilization would take place at the 15-position.

MacDonald-type (*i.e.* 2 + 2) condensation of 1,9-diformyl-5-oxodihydrodipyrrin[8] with 5-*tert*-butyl-2,8-diethyl-3,7-dimethyldihydrodipyrrin-1,9-dicarboxylic acid‡ followed by basic treatment resulted in formation of the 15-*tert*-butyl-5-oxophlorin **1** in 43% yield. Exposure of compound **1** to air in CH_2Cl_2 and daylight (which accelerated the transformation) afforded the neutral π-radical **2** of 15-*tert*-butyl-5-oxophlorin§ in 90% yield. This compound possesses a Soret band at 410 nm and a typical organic π-radical EPR signal at 3000 G. The magnetic susceptibility of **2**, measured by the NMR Evans method[9] is μ_{eff} = 2.5 μ_B at 297 K, indicating that the compound exists entirely in the form of the neutral π-radical.[4]¶ This oxophlorin radical is stable to air for long periods of time in the solid form. It was found to be fairly stable in solution, showing only about 30% decomposition over two weeks in the presence of oxygen (to form 15-*tert*-butyl-15-hydroxy-5-oxophlorin **3**). Addition of acid to a CH_2Cl solution of **2** generated, *via* the readily reduced π-cation porphyrin radical,[10] the diprotonated hydroxyporphyrin **4** (Scheme 1). This reduction–protonation process could be followed by spectrophotometry, which showed clean isobestic points (at λ_{max} = 438 and 540 nm), furthermore demonstrating the quantitative radical character of **2**.

Fuhrhop had earlier demonstrated that the spin density distribution in 5-oxophlorin radicals lies predominately on the carbon atom at the 15-position.[6] By analogy, the free radical in **2** is also believed to be localized preferentially at the 15-position where it can be stabilized by hyperconjugation through the *tert*-butyl substituent.

In order to establish the effect of steric congestion upon the radical formation resulting from the interaction of the 15-substituent with abutting groups in the 13- and 17- positions, synthesis of 12,13,17,18-unsubstituted-15-*tert*-butyl-5-oxophlorin **5** was attempted using the same pathway as described for **1**.‖ This synthesis, however, yielded two products neither of which was a π-radical. The first product was characterized as 15-*tert*-butyl-15-iso-5-oxophlorin **6**** and the second was shown to be the 15-*tert*-butyl-15-hydroxy derivative **7**.†† Structure **7** presents evidence for the trapping of the π-radical at the 15-position (presumably by dioxygen) and further indicates the preferential localization of the radical at this position. A 15-peroxo bis(5-oxophlorin) derivative has been proposed earlier by Fuhrhop *et al.*[6a] The molecular structures of **6**‡‡ and **7**‡‡ were confirmed by X-ray crystallography (Fig. 1). Both macrocycles exhibit a slightly ruffled conformation with a mean deviation from there least-squares plane for the 24 core atoms of 0.263 Å for compound **6** and of 0.257 Å for compound **7**. The C=O bond length for structures **6** and **7** are 1.239 and 1.242 Å, respectively, in good agreement with expected C=O bonds lengths. For compound **7** the C–O bond length in the 15-position is 1.455 Å which is also in agreement with expected normal C–O bond lengths.



Scheme 1

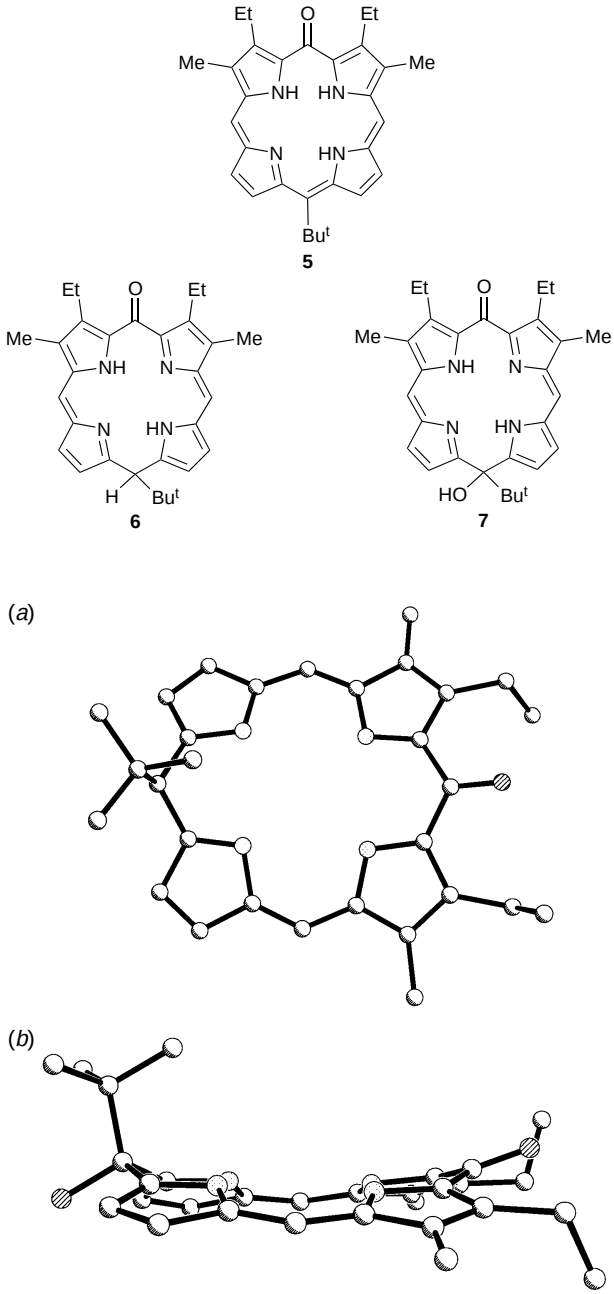


Fig. 1 Molecular structure of (*a*) 15-*tert*-butyl-15-iso-5-oxophlorin **6** and (*b*) 15-*tert*-butyl-15-hydroxy derivative **7**

This work was supported by a grant from the National Science Foundation (CHE-96-23117). Mass spectrometric analyses were performed by the University of California, San Francisco, Mass Spectrometry Facility (A. L. Burlingame, Director) supported by the Biomedical Research Technology Program of the National Center of Research Resources, NIH NCRR BRTP 01614.

Footnotes

† E-mail: smith@chem.ucdavis.edu

‡ Prepared by acidic condensation of trimethylacetaldehyde (TMA) with 2 equiv. of the corresponding α-free-pyrrole benzyl ester (K-10 clay catalyst, CH_2Cl_2–TFA (5 : 1), room temp., 4 d, chromatographed on silica gel eluted with CH_2Cl_2, deprotection with Pd-C/H_2, overall yield 35%).

§ Mp 180–182 °C. UV–VIS $\lambda_{max}(CH_2Cl_2)$/nm 410 (ε 66 700), 628 (11 700), 664 (11 000). ^{1}H NMR (300 MHz, $CDCl_3$–[^{2}H]TFA) δ 1.48 (s, 9 H, Bu^t), 1.56 (t, 6 H, CH_2CH_3), 1.69 (t, 6 H, CH_2CH_3), 3.26 (s, 6 H, CH_3), 3.43 (s, 6 H, CH_3), 3.89 (m, 8 H, CH_2CH_3), 10.06 (s, 2 H, meso-H). MS: *m/z* 550.

¶ The magnetic susceptibility of the free radical was determined using Evans method.[9] Paramagnetic shifts of tetramethylsilane were determined for 2-4 × 10^{-3} m free radical solutions in chloroform and were obtained on a JEOL GSX 400 MHz (^{1}H NMR) spectrometer. At 24 °C, the molar magnetic susceptibility was 2.6 × 10^{-3} cm^{-3} mol^{-1} and the calculated magnetic moment was 2.5 μ_B. Diamagnetic corrections were estimated from Pascal's constants.

‖ The 5-*tert*-butyl-3,7-di-unsubstituted half was prepared by condensation of TMA with 40 equiv. of pyrrole catalysed by TFA.[11]

** Mp 280–285 °C. UV–VIS $\lambda_{max}(CH_2Cl_2)$/nm 420 (ε 86 000), 644 (14 000). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (m, 6 H, CH_2CH_3), 1.25 (s, 9 H, Bu^t), 2.17 (s, 6 H, CH_3), 2.76 (m, 4 H, CH_2CH_3), 3.92 (s, 1 H, 15-meso H), 6.39 (s, 2 H, β-H), 6.81 (s, 2 H, β-H), 6.94 (s, 2 H, meso-H), 12.89 (br s, 2 H, NH). MS: *m/z* 467.

†† Mp 244–246 °C. UV–VIS $\lambda_{max}(CH_2Cl_2)$/nm 448 (ε 66 000), 510 (11 500). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (m, 6 H, CH_2CH_3), 1.53 (s, 9 H, Bu^t), 2.15 (s, 6 H, CH_3), 2.78 (m, 4 H, CH_2CH_3), 6.65 (s, 2 H, β-H), 6.84 (s, 2 H, β-H), 6.97 (s, 2 H, meso-H), 12.95 (br s, 2 H, NH). MS: *m/z* 483.

‡‡ *Crystal Data* for **6**: single crystals (purple) crystallized from MeOH–THF–H_2O, triclinic space group *P*$\bar{1}$, cell dimensions: *a* = 9.765(2), *b* = 11.719(2), *c* = 12.013(2) Å, α = 83.70(3), β = 68.72(3), γ = 81.20(3)°, *V* = 1263.8(4) Å^3, *Z* = 2. X-Ray diffraction data were collected at 130(2) K, λ(Cu-Kα) = 1.54178 Å, θ/2θ scan mode to $2\theta_{max}$ = 114°. Of 4882 reflections measured (±*h*,±*k*,+*l*), 3404 were unqiue and 2425 had $I > 2\sigma$. The structure was solved by direct methods and refined on F^2 using all data by full-matrix least-squares methods (SHELXL-94). Final *R* factors for observed data are *R* = 0.0569 and w*R*2 (all data) = 0.1472. For **7**: single crystals (green) crystallized from MeOH–THF–H_2O, triclinic space group *P*$\bar{1}$, cell dimensions: *a* = 10.154(2), *b* = 11.344(2), *c* = 12.285(2) Å, α = 82.63(3), β = 66.93(3), γ = 78.37(3)°, *V* = 1273.3(4) Å^3 and *Z* = 2. X-Ray diffraction data were collected at 130(2) K, λ(Cu-Kα) = 1.54178 Å, θ/2θ scan mode to $2\theta_{max}$ = 114°. Of 3707 reflections measured (±*h*,±*k*,+*l*), 2365 were unique and 1833 had $I > 2\sigma$. The structure was solved by direct methods and refined (based on F^2 using all data) by full-matrix least-squares methods (SHELXL-94). Final *R* factors for observed data are *R* = 0.0615 and w*R*2 (all data) = 0.1662. 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 182/332.

References

1 C. Adamo, V. Barone and A. Fortunelli, *J. Chem. Phys*., 1995, **102**, 384; A. Hudson, D. Waterman and A. Alberti, *J. Chem. Soc., Perkin Trans. 2*, 1995, 2091.
2 C. D. Bryan, A. W. Cordes, R. M. Fleming, N. A. George, S. H. Glarum, R. C. Haddon, R. T. Oakly, T. T. M. Palstra, A. S. Perel, L. F. Schneemeyer and J. V. Waszczak, *Nature*, 1993, **365**, 821; D. Luneau, J. Laugier, P. Rey, G. Ulrich, R. Ziessel, P. Legoll and M. Drillon, *J. Chem. Soc., Chem. Commun*., 1994, 741; A. W. Cordes, R. C. Haddon and R. T. Oakley, *Adv. Mater*., 1994, **6**, 798.
3 A. F. Fontan, R. J. Kolt, Y. Q. Huang and D. D. M. Wayner, *J. Org. Chem*., 1994, **59**, 4671.
4 E. I. Ochiai, *J. Chem. Educ*., 1993, **70**, 128; I. Morishima, H. Fujii and Y. Shiro, *Inorg. Chem*., 1995, **34**, 1528.
5 A. H. Jackson, G. W. Kenner and K. M. Smith, *J. Chem. Soc. (C)*, 1968, 302; R. G. Khoury, L. Jaquinod, D. J. Nurco and K. M. Smith, *Chem. Commun*., 1996, 1143.
6 J.-H. Fuhrhop, S. Besecke, J. Subramanian, C. Mengersen, D. Riesner and D. Mauzerall, *J. Am. Chem. Soc*., 1975, **97**, 7141; A. L. Balch, B. C. Noll, S. L. Phillips, S. M. Reid and E. P. Zovinka, *Inorg. Chem*., 1993, **32**, 4730.
7 R. G. Khoury, L. Jaquinod, D. J. Nurco, R. K. Pandey, M. O. Senge and K. M. Smith, *Angew. Chem*., 1996, **108**, 2657.
8 P. S. Clezy, A. J. Liepa and G. A. Smythe, *Aust. J. Chem*., 1970, **23**, 589, 603.
9 D. F. Evans, *J. Chem. Soc*., 1959, 2003.
10 D. C. Borg, J. Fajer, R. H. Felton and D. Dolphin, *Proc. Natl. Acad. Sci. USA*, 1970, **67**, 813.
11 C. H. Lee and J. S. Lindsey, *Tetrahedron*, 1994, **39**, 11427.

Received, 17th October 1996; Com. 6/07076K