Redox Behaviour of Phenolic Porphyrins in Basic Solutions: A Reappraisal[1]

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Phenolic porphyrins **1**, **4**, and **5** form stable phenoxyl radicals **3**, **6**, and **7** in deoxygenated as well as oxygenated basic solutions. Mechanistic schemes are presented, involving coupled disproportionation and conproportionation reactions, that do not require oxygen involvement in the redox processes leading to phenoxyl radicals.

INTRODUCTION

In recent years, we have investigated the redox behaviour of porphyrins *meso-* substituted with phenolic groups.[2] Thus, 5,10,15,20-tetrakis(3,5-di-*t*-butyl-4-hydroxyphenyl)porphyrin **1** undergoes two-electron oxidation to **2** in undegassed, basified solutions.[3] Esr spectroscopy indicates conproportionation between **1** and **2** to yield a stable phenoxyl radical **3**.[4] Spin-trapping studies have suggested oxygen as the oxidant because hydroxyl radicals are formed during the reaction (presumably via the disproportionation of hydrogen peroxide in basic solutions[5]) during this reaction, along with further radicals produced by the attack of OH· on the solvent. Consequently, a reasonable hypothesis has been that oxygen from air is reduced by porphyrin **1** to hydrogen peroxide, and is therefore directly involved in the oxidation of **1** to **2** (see reference 18).

Other *meso*-phenolic porphyrins have shown redox activity in undegassed basic solutions. In particular, esr spectroscopy shows that long-lived radicals **6**[2] and **7**[6] are produced from porphyrins **4** and **5**, respectively, suggesting they may have similar redox chemistries to **1**. However, spin-trapping studies with these porphyrins showed no evidence for reduced-oxygen species (e.g., OH·) or radicals derived from the attack of such species on the solvent. The presence of the spin-trap either supressed aggregation of the porphyrin-phenoxyl radical (i.e., **7**), or led to a reduction in the radical's (i.e., **6**) lifetime.[7]

In the light of these observations, we have re-examined the role of oxygen in the oxidation of phenolic porphyrins **1**, **4**, and **5**. Previously, we had reported[2,7] preliminary experiments in which prior removal of oxygen from reaction mixtures

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gave esr-silent solutions. We now know this to be incorrect.

In this paper, we report that mixing deoxygenated solutions of base and phenolic porphyrin also generates phenoxyl radicals, demonstrating that oxygen is not as central to phenoxyl-radical formation as previously supposed.[5] We also propose redox mechanisms for these phenolic porphyrins that account for these observations.

MATERIALS AND METHODS

Porphyrins **1**, **4**, and **5** were synthesised as reported previously.[3,6] Solutions of porphyrin **1** were prepared in dichloromethane (DCM, $5*10^{-3}$ M) and deoxygenated for several hours using repeated cycles of freeze-pump-thaw under nitrogen on a Schlenk line. One of these solutions contained a 20-fold molar excess (over the porphyrin **1**) of the spin trap phenyl-t-butylnitrone (PBN, 10^{-1} M). Similarly, deoxygenated DCM solutions of porphyrin **5** ($5*10^{-3}$ M) were prepared, while solutions of the highly hydroxylated porphyrin **4** were prepared in deoxygenated methanol ($5*10^{-3}$ M).

To each of these solutions was added a similarly deoxygenated methanolic solution of the base tetra-n-butylammonium hydroxide (tnBAH; Aldrich, 1 M; 2 ml). Aliquots of these deoxygenated mixtures were then canulated into a thoroughly nitrogen-flushed, sealed, quartz esr flat cell, and placed in the cavity of a Varian E-3 esr spectrometer at room temperature (20°C). The instrument was operated at microwave frequency, 9.300 ± 0.005 GHz; field centre, 336.5–337.5 ± 0.1 mT; microwave power, 20 mW; scan-time, 4 minutes; gain 10^4–10^5; time-constant, 0.3 s; 0.1 modulation amplitude; g values were standardised against diphenylpicrylhydrazyl (DPPH, g = 2.0037 ± 0.0002).[8,9]

The time taken from mixing the deoxygenated solutions to recording esr spectra, was in the order of 2–3 minutes. This places a lower limit on the minimum time within which spectra can be accurately recorded after mixing the solutions. Using the Varian instrument, uncertainties in the measurement of field and frequency limit the accuracy of the quoted g values to three decimal places.

Computer simulation of the esr spectrum obtained for the porphyrin phenoxyl radical **7**, was performed on a Viglen Genie 4DX250 Professional Workstation, using a programme written and supplied by D.R. Duling of the Laboratory of Molecular Physics, NIEHS/NIH, North Carolina, USA.

Uv/visible spectroscopy was performed on a Perkin-Elmer Lambda 9 Spectrophotometer, using a sealed, nitrogen-flushed quartz uv/visible cell containing deoxygenated DCM solution (10^{-5} M) of porphyrin **1** to which had been added five drops of the deoxygenated base 1 M tnBAH in methanol.

RESULTS

Previously, we had reported that addition of the undegassed base, 1 M tnBAH in methanol, to undegassed DCM solutions of the porphyrin **1**, gave a rapid (i.e., during 1 minute) series of colour changes – from red to brown to purple to blue. The uv/visible spectrum of the final blue solution was similar to that shown in figure 1d, but without the band at 426 nm.[10,11] In higher concentrations, the blue solution also gave a strong, triplet, esr spectrum.

On addition of deoxygenated base to deoxygenated DCM solutions of **1**, a similar series of colour changes is observed, albeit over a longer period (during 30 minutes). Figure 1 shows the sequence of uv/visible spectral changes over this time.

Mixing deoxygenated solutions of base and porphyrin **1** gave the same esr spectrum as mixing of the undegassed solutions, i.e., a strong triplet assigned to the porphyrin-phenoxyl radical **3** (a_H = 0.133 mT, ΔH_{pp} = 0.053 mT, g = 2.009(6) ± 0.001). Repeating this experiment in the presence of an
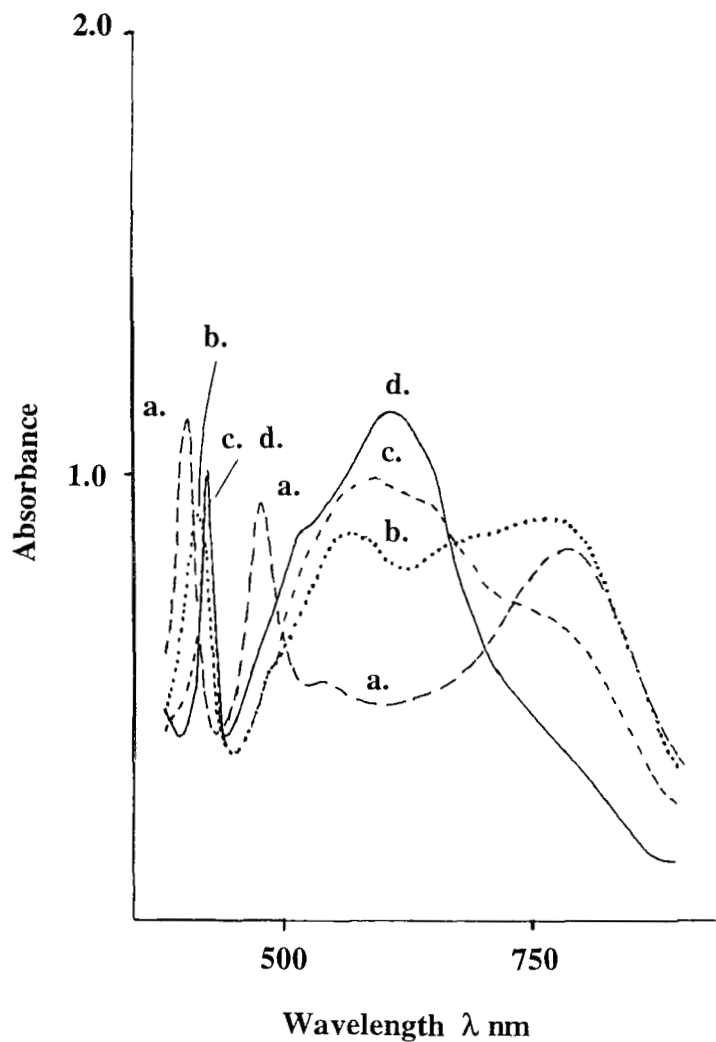
FIGURE 1 Uv/visible spectra obtained during 30 minutes, on addition of deoxygenated *tri*BAH in methanol (1 M; five drops) to a deoxygenated DCM solution of porphyrin 1 (10^{-5} M).

excess of the spin-trap PBN (figure 2) again gave a triplet esr spectrum; this time flanked by weaker bands from a PBN spin-adduct (a_N = 1.48 mT, (a_H = 0.41 mT, g = 2.006(1) ± 0.001). We attribute these weaker bands to hydroxyl radicals, or the radical results of their attack on the solvent,[5] implicating formation of hydrogen peroxide. In base, this is known to disproportionate to hydroxyl radicals that attack the solvent.[5]

Porphyrins 4 and 5 give phenoxyl radicals 6 and 7, respectively, in undegassed basic solutions. Phenoxyl radical 6 exhibits a predominantly triplet esr spectrum with side-bands previously ascribed to ^{13}C-satellites.[6] The phenoxyl radical 7 gives a 15-line esr spectrum that is generated from 5 in undegassed 1 M aqueous KOH only in the presence of the spin-trap (4-pyridyl-1-oxide)-N-*t*-butylnitrone (POBN).[7] Without POBN, this
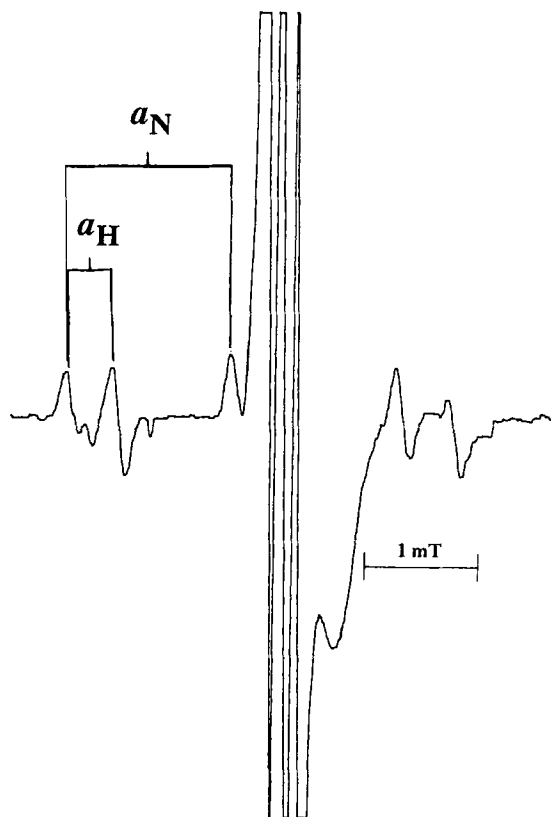
FIGURE 2   Esr spectrum obtained on addition of deoxygenated *tn*BAH in methanol (1 M; 2 ml) to a deoxygenated DCM solution of porphyrin 1 ($5*10^{-3}$ M) containing a 20-fold molar excess of the spin-trap PBN. Spectral parameters for porphyrin: ($a_H = 0.133$ mT; $\Delta H_{pp} = 0.053$ mT; g = 2.009(6) ± 0.001. Spectral parameters for PBN-adduct: $a_N = 1.48$ mT; $a_H = 0.41$ mT; g = 2.006(1) ± 0.001.

radical gives an esr spectrum consistent with aggregation and spin- exchange broadening.[2] We subsequently reported that POBN acts solely to impede aggregation of the radical.

We have found that porphyrins 4 and 5 also generate porphyrin-phenoxyl radicals 6 and 7, respectively, in deoxygenated solutions of the base, 1 M tnBAH in methanol. In particular, the radical 7 gives a 15-line esr spectrum (figure 3a: ($a_{H(1)}$ = 0.153 mT; aH(2) = 0.068 mT; g = 2..006(4) ± 0.001) *without* the necessity of added spin-trap POBN. This spectrum was simulated (figure 3b), as previously reported,[7] by assuming spin-density is localised on a 3,5-dimethoxy-4-phenoxyl *meso*-substituent. We suggest that the

bulky tetra-*n*-butylammonium cation, from the base 1 M *tn*BAH in methanol, is sterically impeding aggregation of the radical 7 in the same way as POBN.[7]

DISCUSSION

Addition of deoxygenated base to a dilute deoxygenated DCM solution of porphyrin 1, produces an initial uv/visible spectrum (figure 1a) consisting of two bands (at 404 and 480 nm, respectively) and a broad feature centred on 787 nm. This spectrum is similar to those obtained on addition of base to *undegassed* solutions of 1 metal complexes which are oxidation inert (e.g., Ni(II), Pd(II), Mn(III), Cu(II), V(IV) = O, Sn(IV)). We have previously shown that, in base, porphyrin 1 undergoes conformational changes that severely distort the macrocycle from planarity, so labilising 1 to oxidation. For the metal complexes just mentioned, we have suggested that the metal interacts with the macrocycle to sterically and electronically impede its labilisation to oxidation.[10a,b]

Figure 1a also resembles the spectrum of oxophlorins.[10c] The interaction of phenoxide *meso*-substituents with the porphyrin pi-system (e.g., 1c in Scheme 1) would produce some formal double-bond character between them, so that the new chromophore would be expected to have some of the spectral features of oxophlorins.

This spectrum then gradually changes, through figures 1b and c, into figure 1d which contains features previously identified[3] as the oxidised porphyrin 2, i.e., a broad, fairly intense band, centred at 610 nm. However, superimposed on this final spectrum is a porphyrin-like B band at 426 nm. This suggests that, under deoxygenated conditions, the final solution contains oxidised porphyrin 2, the phenoxyl radical 3 (more concentrated solutions are esr active) and a small amount of a porphyrin-type compound. We shall return later to the nature of this compound.

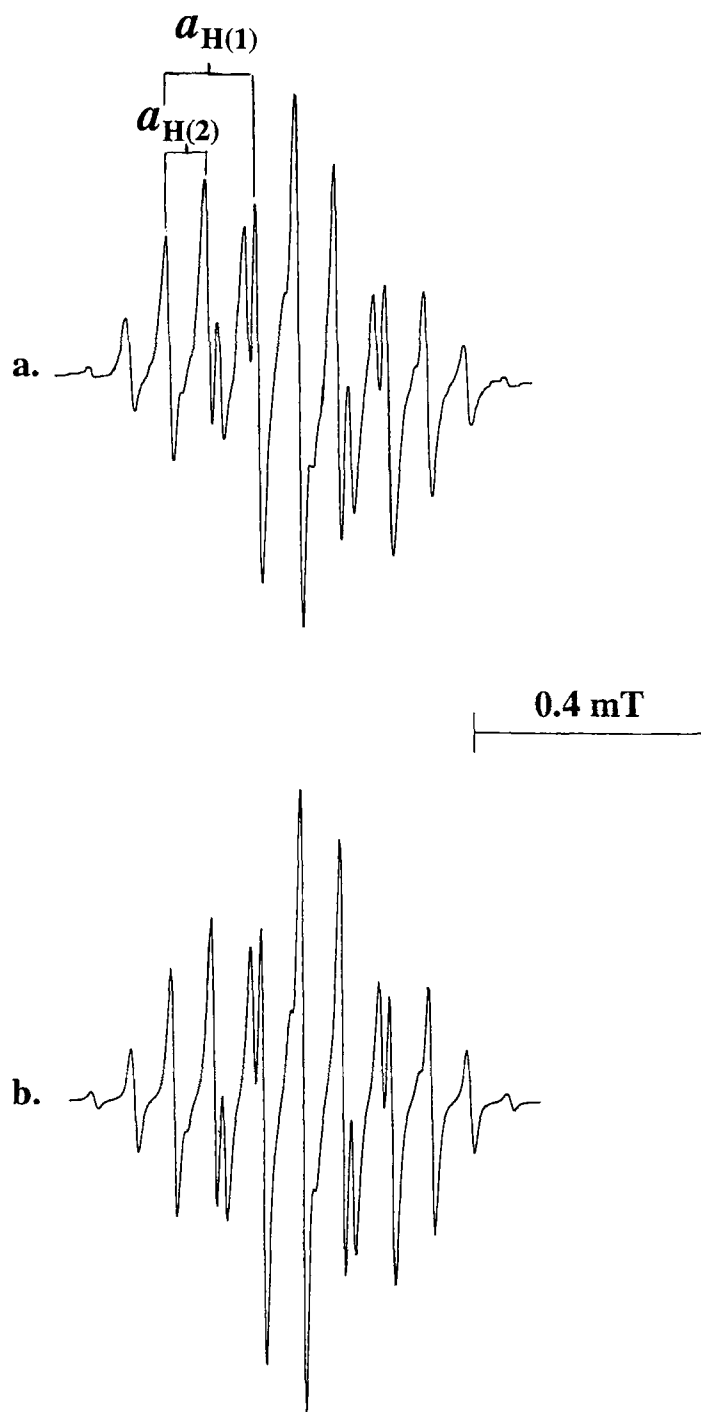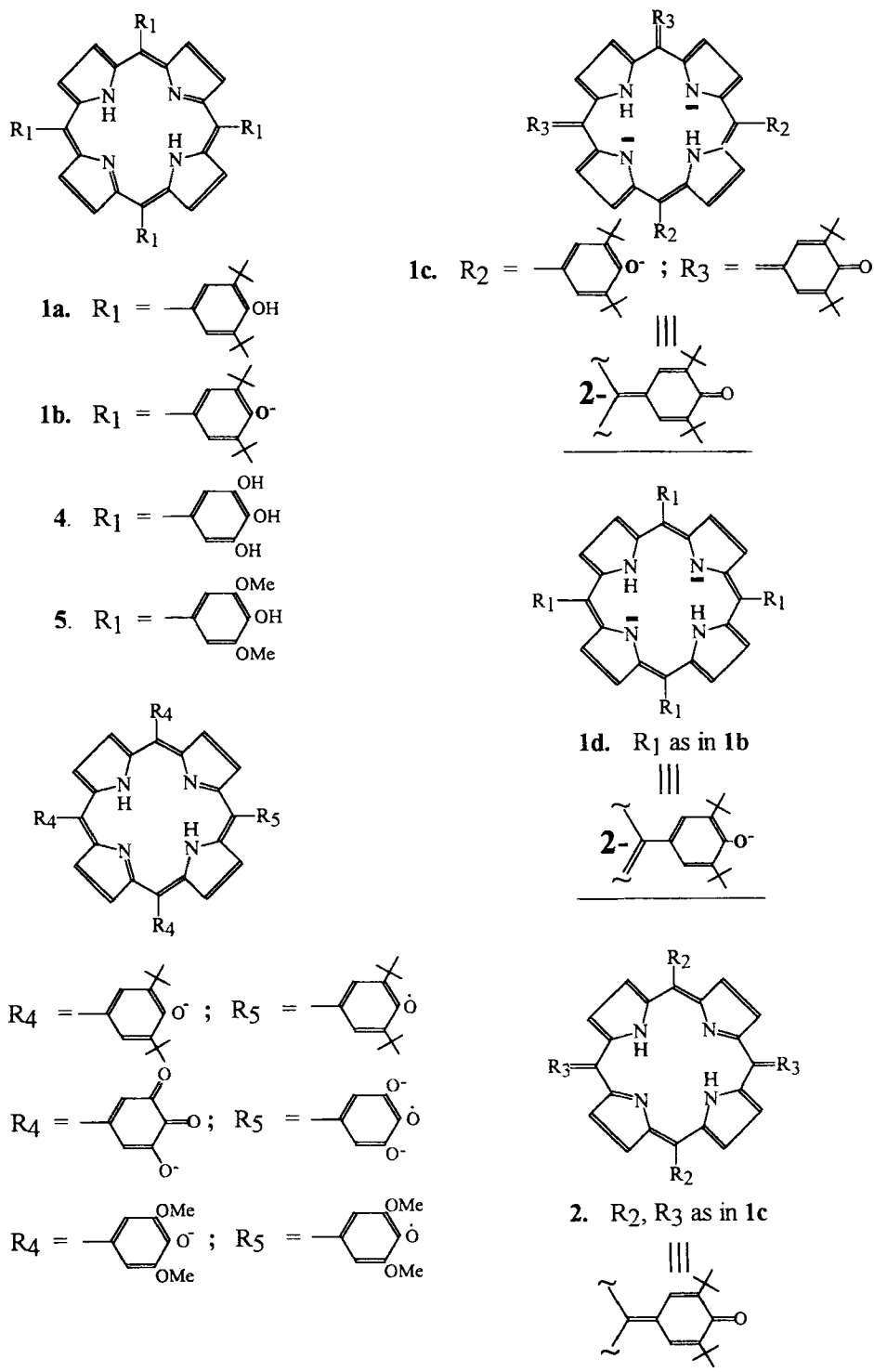The production of long-lived phenoxyl

FIGURE 3 a; Esr spectrum obtained on addition of deoxygenated *tn*BAH in methanol (1 M; 2 ml) to a deoxygenated DCM solution of porphyrin 5 (5*10^{-3} M). Spectral parameters: $a_{H(1)} = 0.153$ mT; $a_{H(2)} = 0.068$ mT; g = 2.006(4) ± 0.001. b; Simulated esr spectrum obtained using the above experimentally-obtained spectral parameters, and assuming unpaired electron localised on a 3,5-dimethoxy-4-phenoxyl *meso*-substituent: $a_{H(2H)} = 0.153$ mT; $a_{H(6H)} = 0.068$ mT; line-width = 0.006 mT; line-shape = 100% Laurentzian.

1a. $R_1 =$

1b. $R_1 =$

4. $R_1 =$

5. $R_1 =$

1c. $R_2 =$; $R_3 =$

2-

1d. R_1 as in **1b**

2-

3. $R_4 =$; $R_5 =$

6. $R_4 =$; $R_5 =$

7. $R_4 =$; $R_5 =$

2. R_2, R_3 as in **1c**

SCHEME 1

radicals, apparently without the need for oxygen,[12] requires reappraisal of the redox mechanism for porphyrins 1, 4, and 5 in 1 M methanolic tnBAH.

For porphyrin 1, our understanding has been that oxygen *directly* oxidises 1b, or 1c, to 2 generating peroxide. Oxidised porphyrin 2 then conproportionates with 1b to produce the phenoxyl radical 3.

We have also shown, by analogy with the known chemistry of anthraquinones,[13] that a further reaction occurs between base and oxidised porphyrin 2.[5] This generates 3, via a short-lived dimer that undergoes homolysis to 2, producing a stoichiometric amount of hydrogen peroxide. The latter, in basic solutions, disproportionates to hydroxyl radicals.[14,15] In this case, the source of hydroxyl radicals is the hydroxyl anion.

We now propose the following mechanism for the production of 3 under anerobic conditions (see Scheme 2).

a) Porphyrin 1 deprotonates in base to the phenoxide 1b, which electronically rearranges to 1c

(this accounts for the uv/visible spectrum shown in figure 1a).

b) Without a central metal to lock its conformation,[10b] 1c slowly disproportionates to the oxidised porphyrin 2 and *reduced* porphyrin 1d (uv/visible spectra figures 1b and 1c).

c) Oxidised porphyrin 2 then forms phenoxyl radical 3 by two routes:-

(i) conproportionation with 1c, and,

(ii) via a reaction with base that also generates a small amount of hydroxyl radicals from the stoichiometric amount of hydrogen peroxide produced.

In the absence of oxygen, reduced porphyrin 1d is attacked, either by hydroxyl radicals or by small amounts of water in the solvent (produced during the original deprotonation step). The former produces 1, which is immediately converted to 1c (and disproportionates, etc), while the latter converts 1d to a chlorin (probably via a phlorin intermediate[16]). We suggest this is the cause of the band at 426 nm in Figure 1d. Unlike 1b, the reduced pyrrole ring makes the chlorin

[O] = O$_2$ (in air) or H$_2$O$_2$ (deoxygenated)
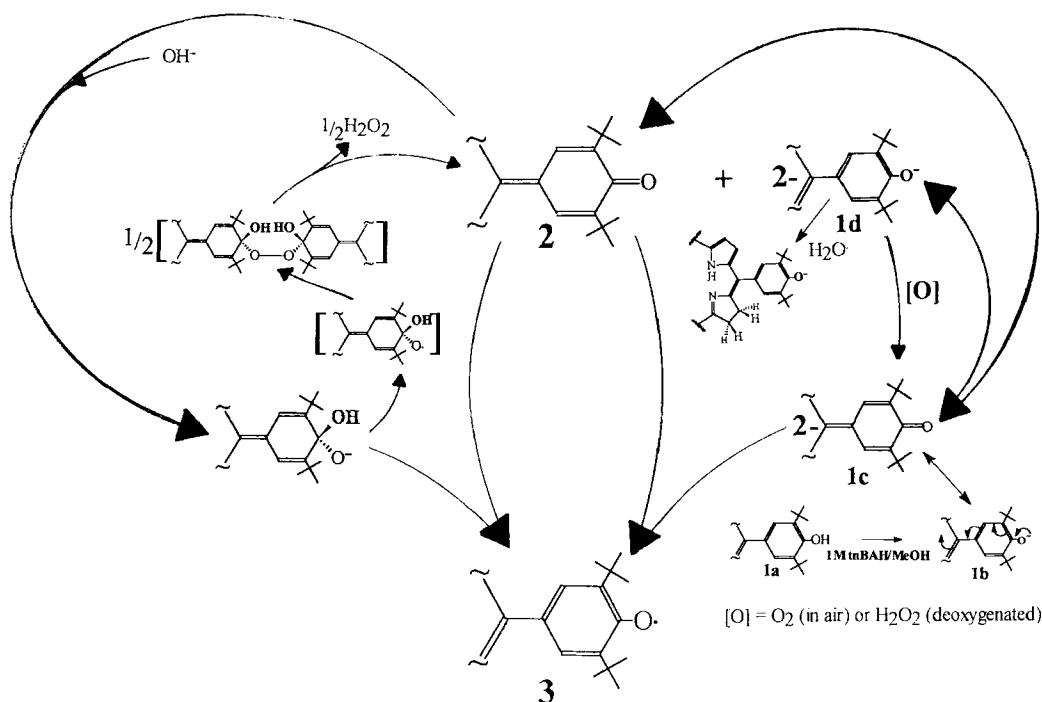
SCHEME 2

less able to delocalise phenoxide negative charge onto its macrocycle. Consequently, the uv/visible spectrum of the chlorin in base will not show oxophlorin-type features, but will have a B band.

By contrast, in the presence of excess oxygen, either **1b** or **1c** are directly oxidised to **2** as before, or **1d** is rapidly reoxidised back to **1** (which, as **1c**, disproportionates to **1d** and **2** again) in competition with attack of solvent to form a chlorin. In either case, this produces a much higher level of **2**, making for fast generation of **3**, via conproportionation with **1c**.

A variation on Scheme 2 might explain the production of phenoxyl radical **7** (see Scheme 1 and Figure 3) from porphyrin **5**. However, the following observations must first be noted.

a) In basic solutions, 5 does not undergo the same extensive oxidation as 1. Thus, large-scale production of an oxidised porphyrin analogous to 2 is not observed.[2]

b) On addition of base, 5 gives deep green solutions with uv/visible spectra showing a porphyrinic B band.[7] This is red-shifted compared to the neutral porphyrin, whose spectrum is largely regenerated on neutralisation of these basic solutions.

c) Unlike 1, the phenoxide of 5 may be alkylated with a variety of alkyl groups. to generate *meso*-tetrakis(alkoxyphenyl)porphyrins. This suggests that in 5, delocalisation of phenoxide negative charge onto the macrocycle is not as extensive as in 1, leading to less disproportionation of the phenoxide.

d) Some reaction of 5 clearly does occur in base,[2,7] as evidenced by the production of phenoxyl radical 7 (though not to the same extent as 3 – the instrument gain needed to observe 7 is about ten times greater than for 3). That no evidence for hydroxyl radicals can be found by spin-trapping, indicates that hydrogen peroxide, if formed, is probably only present in trace quantities.

In terms of a mechanism analogous to Scheme 2,

these observations may be rationalised as some disproportionation of **5** in base to form a small amount of an oxidised and reduced porphyrin. The reverse reaction back to **5** is, however, more highly favoured (thus removing the reduced porphyrin), but the oxidised porphyrin can also react with **5** to generate the phenoxyl radical **7**.

Further reaction of the oxidised porphyrin with base (by analogy with the left-hand branch of scheme 2) could conceivably lead to more **7**. However, Sawyer *et al.* have shown[13] that hydroxide nucleophilic addition to quinone carbonyl groups is less favoured by electron-donating neighbouring groups, e.g., in this case methoxy groups. Consequently, the equilibrium concentration of adduct formed between base and the oxidised porphyrin (itself in low concentration) from **5**, is expected to be low. Production of **7**, by reaction of this adduct with the oxidised porphyrin, is therefore not favoured. Even less likely is the formation of a peroxo-dimer capable of homolysis back to the oxidised porphyrin and hydrogen peroxide. This would account for the lack of spin-trapped radicals.

We had earlier shown that in undegassed basic solutions, porphyrin **4** gives a phenoxyl radical **6** which has seven electrons fewer than **4**.[6] In this work, the same radical is produced in deoxygenated solutions of base. Again, a mechanistic scheme can be envisaged in which disproportionation of an electronically-rearranged porphyrin yields both oxidised and reduced porphyrins. However, **4** differs from **1** and **5** in that the same pyrogallyl *meso*-substituent, after deprotonation, can donate electron density *twice* onto the macrocycle (Scheme 3a), leaving a quinonyl *meso*-substituent. Following disproportionation, the oxidised porphyrin still has an intact macrocycle: oxidation has occurred preferentially at a *meso*-substituent to form *a porphyrin with a quinonyl group*. This new porphyrin can, in turn, undergo electronic rearrangement and disproportionation to an oxidised and reduced porphyrin: the former is now a porphyrin with *two* quinonyl *meso*-substituents, while the latter is the *regenerated*
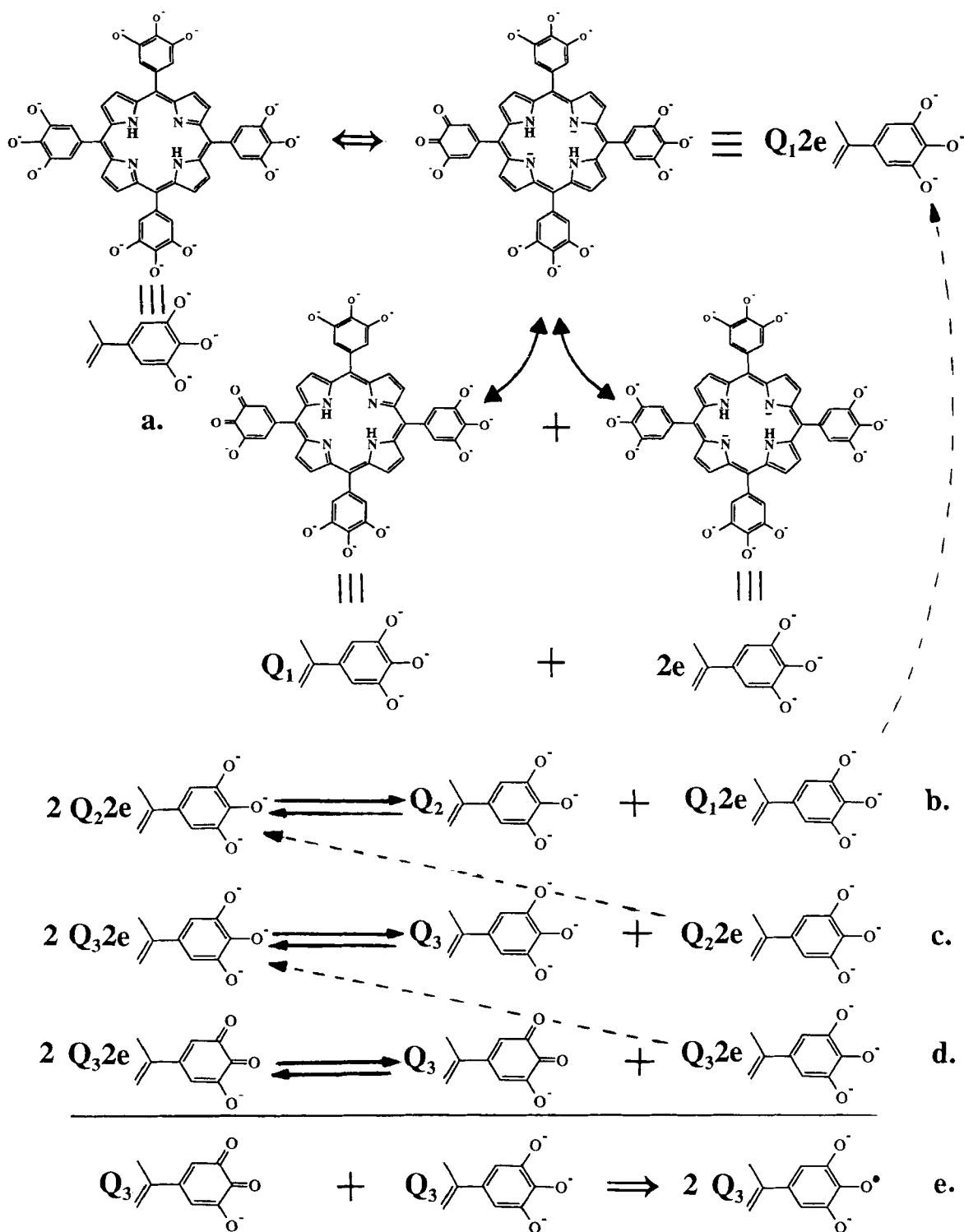
SCHEME 3

starting porphyrin (Scheme 3b). Further dispropor-tionation reactions can be envisaged (Scheme 3c-d) which continue until a porphyrin with four quinonyl *meso*-substituents is formed. This then conproportionates with the previously formed three quinonyl- substituted porphyrin to give the radical **6** (Scheme 3e). Thus the driving force for *this* cascade of disproportionation reactions would be the switching of electron density be-tween *meso*-substituents and porphyrin macro-cycle that allows retention of the porphyrin aromaticity and quinone-substituent formation.

As with porphyrin **5**, there is no evidence (via spin-trapping) of hydroxyl radical formation, pre-sumably because hydroxide nucleophilic addition to quinone carbonyl groups with hydroxide neighbouring groups is more likely to lead to complex rearrangements and/or fragmentations of the quinonoid six-membered carbocycle.[17]

In conclusion, our results clearly show that the redox activity of phenolic porphyrins is not as oxygen-dependent as previously supposed.[18] In this respect, phenolic porphyrins could be said to echo the aerobic (e.g., haems) and anaerobic (e.g., cobyrinic acid) redox versatility of the naturally-occurring tetrapyrrolic macrocycles.[19]

Acknowledgements

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