C–H Bond activation by alumina: facile hydroxylation of chlorins at their saturated β-carbon by molecular oxygen and alumina

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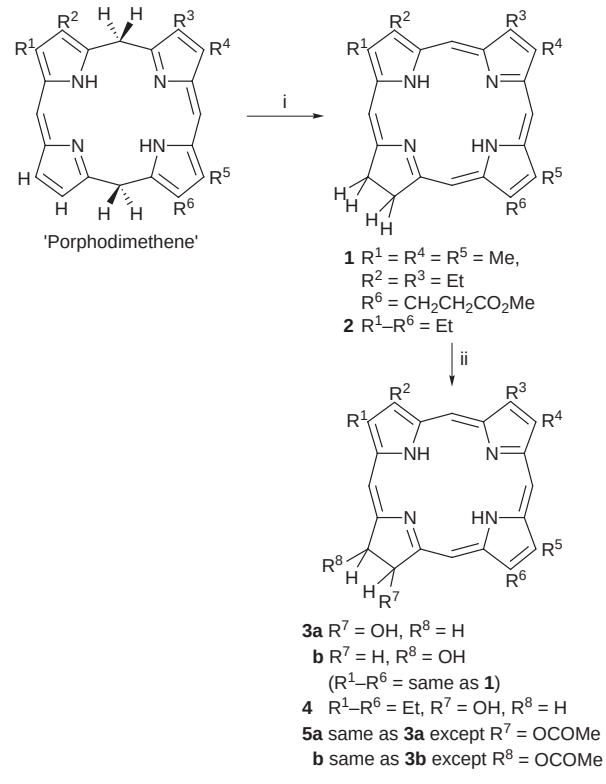
The mono-hydroxylation of a β-methylene carbon in the pyrroline ring of a chlorin requires only alumina and molecular oxygen as reagents, with good yields (70–80%) of the hydroxy chlorin obtained at room temperature in 2 h; this is the first example of a hydroxylated chlorin that has been prepared in a regiospecific manner starting from a chlorin, and the first demonstration of the mild activation of a C–H bond by alumina for its oxidation into a hydroxy group.

Chlorins serve as prosthetic groups for proteins that perform a diverse set of biological functions. Magnesium chlorins (chlorophylls) are found in the photosynthetic proteins of green plants.[1] Iron chlorins are the prosthetic groups for a number of redox proteins, such as the heme in sulfmyoglobin,[2] in the green catalases from *Neurospora crassa* and *Escherichia coli*,[3] as well as the heme (heme *d*) in cytochrome *d* of *E. coli*.[4] Additionally, several dihydroporphyrins have been isolated from marine organisms, such as the sex-differentiating pigment, bonellin, as well as (possible antioxidants) tunichlorin, cyclopheophorbide and chlorophyllone *a*.[5] Like porphyrins, the hydroporphyrins are ubiquitous in nature.

A major thrust of our efforts has been the development of facile methods to prepare the chlorin macrocycle in a regioselective manner directly from linear tetrapyrroles, and also to develop useful pathways for their further elaboration. In this latter vein, we now report the facile mono-hydroxylation of chlorins **1** and **2** (Scheme 1) on their β-methylene carbons in the pyrroline ring. Hydroxylated chlorins are of interest because the iron chlorin prosthetic group of the bacterial oxidases, heme *d*, is thought to contain a bis-hydroxylated pyrroline ring.[4] The hydroxy functional group modifies the heme *d*'s π-system, enabling it to more strongly bind molecular oxygen than heme *b* (protoheme),[6] and presumably making it less prone to oxidation. Additionally, hydroxylated chlorins have elicited interest because they exhibit potential as PDT agents.[4b] The new and simple oxidation reported here represents the first example of a hydroxylated chlorin that has been prepared in a regiospecific manner starting from a chlorin.§ Even more interesting, these results are the first demonstration of the mild activation of a C–H bond by alumina for its oxidation into a hydroxy group.¶

Preparation of chlorins **1** and **2** *via* rearrangement of their metallated porphodimethenes,[9] occurred in a regioselective manner (*i.e.* only one pyrroline ring isomer produced), as shown in Scheme 1. Monohydroxylation of chlorin **1** furnished chlorins **3a**,**b**, while mono-hydroxylation of the more symmetrically substituted chlorin **2** furnished only the one chlorin **4**. In each case, oxidation was confined to the pyrroline ring. The oxidation′s experimental procedure was simple and straightforward. A column was prepared with a slurry of Grade 3 alumina gel,‖ and a solution of the chlorin was allowed to penetrate the alumina gel column to maximize the surface area of adsorption. The mixture was allowed to stand for 2 h, whereupon the hydroxylated chlorin was eluted off the column. This remarkable oxidation of the β-carbon resulted in 70–80 % yields of the mono-hydroxylated chlorin, with little oxidation of the macrocycle to porphyrin. While chlorin isomers **3a** and **3b** were not separated efficiently by chromatography, isomer **3a** crystallized out of hexane–EtOAc in preference to **3b** (as determined by a difference NOE experiment).

The hydroxylated chlorin **3a** was characterized by IR, UV–VIS and NMR spectroscopy and high resolution mass spectrometry and elemental analysis, as well as by chemical transformation (*vide infra*).** The 400 MHz ^{1}H NMR spectrum of chlorin **1** in $CDCl_3$ exhibited a singlet proton resonance at δ 4.60, indicative of the four hydrogens on the pyrroline ring.[9] The substitution of a pyrroline ring hydrogen with a hydroxy group produced a spectrum that exhibited three new resonances for the three remaining protons on the pyrroline ring, which resonated as doublets of doublets at δ 6.60, 4.78 and 4.38, while the hydroxy proton resonated as a broad singlet at δ 2.61. The COSY spectra of chlorin **3a** (Fig. 1) clearly shows that the three proton resonances at δ 6.60, 4.78 and 4.38 are coupled to each other, as would be expected from the three protons on the pyrroline ring. Further corroboration of the structure of chlorin **3a** came from a comparison of the DEPT spectra of chlorin **1** and **3a** (Fig. 2). The spectra exhibit similar methoxy ester and ring methyl and methylene substituent ^{13}C resonances at δ 52.0 and < 22, respectively. The difference in the resonances of the pyrroline ring β-carbons was striking, however. Chlorin **1** exhibited three methylene resonances between δ 36–38, indicative of the two pyrroline ring β-carbon methylenes and



Scheme 1 *Reagents and conditions*: i, $Zn(OAc)_2$, 65 °C; ii, Al_2O_3, O_2, 25 °C

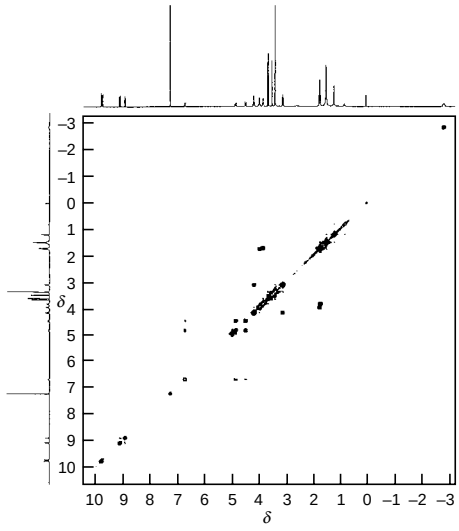


Fig. 1 400 MHz COSY spectrum of chlorin **3a** ($CDCl_3$)

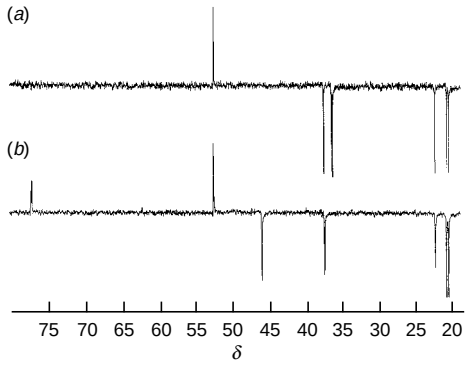


Fig. 2 100.5 MHz DEPT spectra ($3\pi/4$ pulse angle) of chlorins (*a*) **1** and (*b*) **3a** ($CDCl_3$). Peaks directed up are due to methyl and methine carbons, peaks directed down are due to methylene carbons.

the propanoate methylene adjacent to the carbonyl. While chlorin **3a** exhibited a similar propanoate methylene resonance at δ 37, the pyrroline ring β-carbon ^{13}C resonances were markedly shifted downfield. The one remaining methylene β-carbon exhibited a resonance at δ 45, and the carbon that contained the hydroxy functional group exhibited a new methine resonance at δ 77.

The mechanism of the oxidation is not well understood. The mono-hydroxylation of chlorins **1** or **2** required the presence of both alumina and molecular oxygen; no reaction occurred when the solvent was degassed with argon and the column packed and run in a glove box. Zn-chlorins were hydroxylated in the same manner as free-base chlorins, and the reaction took place in the dark. Bis-hydroxylation was not observed, even when the chlorins were left on the alumina for extended periods of time (at room temperature). One might speculate that in the tight confines of the basic alumina surface, adsorbed chlorin could be deprotonated at the pyrroline ring.†† Reaction of the newly formed chlorin anion with correctly positioned adsorbed triplet oxygen to form the chlorin radical, followed by recombination with a hydroxyl radical, is a scenario similar to the much slower, basic solution oxidation (allomerization) observed with chlorophyll *a*. The latter mechanism requires formation of an (exocyclic ring) enolate that reacts with triplet oxygen to form the chlorophyll radical, which then recombines with a hydroxyl radical to form the 13^2-hydroxy chlorophyll derivative.[11] Recombination of the chlorin radical with triplet oxygen to form the peroxyl radical, followed by decomposition to form the hydroxy group, cannot be ruled out. However, in the allomerization of chlorophyll *a*, this leads to the formation of a carbonyl and not a hydroxy functional group. While there are literature examples of hydroxy groups that undergo addition to alkenes and epoxides in the presence of alumina,[7] there is no precedence for the hydroxylation of an unfunctionalized carbon.

The hydroxylated chlorins were stable to air oxidation (unlike chlorin **1**, which slowly formed porphyrin), and stable to high temperatures under vacuum. Under strongly acidic conditions (H_2SO_4, MeOH), chlorin **3a** was slowly transformed into porphyrin (half-life of 24 h), presumably *via* loss of water. The Zn-metallochlorin was easily formed, and demetallation with TFA produced no porphyrin. Due to the apparent stability of chlorins **3** and **4**, it was anticipated that the hydroxy function could be utilized to allow for the further elaboration of the chlorin macrocycle. As an initial attempt, acetylation of a mixture of **3a** and **3b** (Ac_2O, pyridine, 10 mol% DMAP) furnished chlorins **5a** and **5b** (Scheme 1) in 95% yield. The production of **5**, which exhibited a pyrroline ring methine ester proton resonance at δ 7.65, and an acetate methyl proton resonance at δ 2.20, was additional proof for the structure of the hydroxy chlorin. Further study of the chemistry of hydroxy chlorins and their derivatives, and their use in the preparation of more complex molecules, is an ongoing project in our group.

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Notes and References

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§ Vicinal bis-hydroxy chlorins have been prepared from porphyrins with OsO_4. The formation of the bis-hydroxy chlorins in this manner produces four regioisomers when starting from asymmetrically substituted porphyrins (ref. 4).

¶ The utilization of alumina for the oxidation of hydroxy compounds (ref.7) or the dehydrogenation of arenes (ref. 8) required an oxidant other than oxygen, or a transition metal catalyst plus oxygen.

‖ The oxidation reaction has been accomplished with several different batches of neutral alumina (60–325 mesh), received from Fisher Scientific.

** The IR spectrum of chlorin **1** exhibited only one absorption above 3000 cm^{-1} at 3345 cm^{-1}, indicative of the N–H stretch, while the hydroxy chlorin **3a** exhibited two absorptions above 3000 cm^{-1}, one at 3342 (with a shoulder at 3430) cm^{-1} and a second, weaker absorption at 3586 cm^{-1}, indicative of the N–H and O–H stretches, respectively. The UV–VIS spectrum of chlorin **3a** shows a small (10 nm) hypsochromatic shift of the Q band relative to chlorin **1**. Both HRFABMS and elemental analysis were consistent with the hydroxy chlorin.

†† Deprotonation of the pyrroline hydrogens on tetraphenylchlorin occurs with *tert*-butoxide (ref. 10).

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