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Bilitrienones from the chemical oxidation of dodecasubstituted porphyrins

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ABSTRACT

The structure of the ring-opened product from direct oxidation of *meso*-tetra-arylporphyrins has been controversial for three decades. Herein we show that bilitrienones **2** are obtained from oxidation of metal-free dodecasubstituted porphyrins **1** in the presence of sodium nitrite, trifluoroacetic acid, and air oxygen. The presence of the *para*-nonyl groups in **1b** stabilized the corresponding bilitrienone **2b**, which was characterized by X-ray crystallography. In the absence of the *para*-nonyl groups bilitrienone **2a** undergoes a rapid hydration reaction, giving biladienone **3a** as the major isolated product. The molecular structures of **2b** and **3a**, and the photochemical isomerization of **3a** are discussed.

1. Introduction

The *meso*-oxidation of metalloporphyrins and -chlorins has been investigated for several decades in order to gather insight into the important biological processes of heme catabolism,[1] chlorophyll degradation,[2] and formation of algal biliproteins.[3] The open-chain oxygenated tetrapyrroles, often designated generically as bile pigments, perform important biological functions, for example, as the chromophores in biliproteins,[4–6] and have been proposed for various applications, including as antiviral and antioxidant agents.[7–9] In living organisms, bile pigments (e.g., biliverdins) are formed from the highly specific enzymatic oxidation of heme, catalyzed by heme oxygenase.[10,11] On the other hand, the chemical syntheses of bile pigments can be achieved from pyrromethenone[12–14] or dipyrromethene synthons,[15] or from chemical oxidation of porphyrins and metalloporphyrins using O_2 in the presence of ascorbic acid or hydrazine (so-called coupled oxidation of iron porphyrins),[16,17] thallium(III) or cerium(IV) trifluoroacetate salts,[18–20] N_2O_4[21] or sodium nitrate and trifluoroacetic acid,[22] hydrogen peroxide[23] or *meta*-chloroperoxybenzoic acid (mCPBA) in pyridine,[24] by reactions of metalloporphyrin π-cation radicals with nucleophiles,[25] or from photo-oxygenation.[26–28] Whereas the structures of the oxidation products from β-octasubstituted porphyrins (e.g., octaethylporphyrin and protoporphyrin-IX) are well documented and were shown to involve the formation of formyl-bilitrienones, those from the related *meso*-substituted porphyrins, such as *meso*-tetraphenylporphyrin (TPP), have been subject of controversy for over three decades. The first spectral evidence for the formation of a bilitrienone from TPP was reported in 1980 by one of us.[26] This compound was presumably unstable and rapidly underwent reversible addition of water, methanol or ethanol at the a-methine carbon bridge, forming the corresponding biladienones.[28] Indeed, the involvement of a bilitrienone intermediate was controversial, since no NMR data were available for this product or its metal complexes. More recently, during our investigation of the oxidative ring-opening reaction of dodecasubstituted porphyrin **1**, we isolated and characterized the air- and solvent-stable Ni(II), Zn(II) and Cu(II) complexes of its corresponding bilitrienone.[22,24]

2. Results and discussion

The chemical oxidation of dodecasubstituted porphyrin **1a** using 6 equiv of $NaNO_2$/TFA in the presence of air gave the corresponding benzoylbiliverdin **2a**, which was too unstable to isolate in pure form, due to its readily hydration to produce **3a**.[22,24] Two distinct isomers of **3a**, purple and pink in color, were isolated in about 3:1 ratio after workup of the oxidation reaction and purification by column chromatography. Both isomers showed broad absorption bands in the UV–vis, indicating significant conformational flexibility. Mizutani and co-workers have also isolated the purple and pink fractions upon chemical oxidation of iron (II)-TPP and reported that the pink benzoylbiliverdin could be photoisomerized to the purple benzoylbiliverdin, while the reverse isomerization did not proceed.[29] Heating the mixture of isomers **3a** in the presence of a metal salt results in dehydration and metalation with formation of the corresponding stable metal complexes of **2a**.[24] Under the same conditions, porphyrin **1b** was also oxidized, but in this case benzoylbiliverdin **2b** was more resistant to spontaneous hydration than **2a**, and was therefore isolated successfully in 70% yield, along with 15% yield of the corresponding hydrated form **3b**. Previous studies by Smith,[26] Fuhrhop,[20] and Cavaleiro[28] have shown that TPP is oxidized to give the corresponding biliverdin which rapidly

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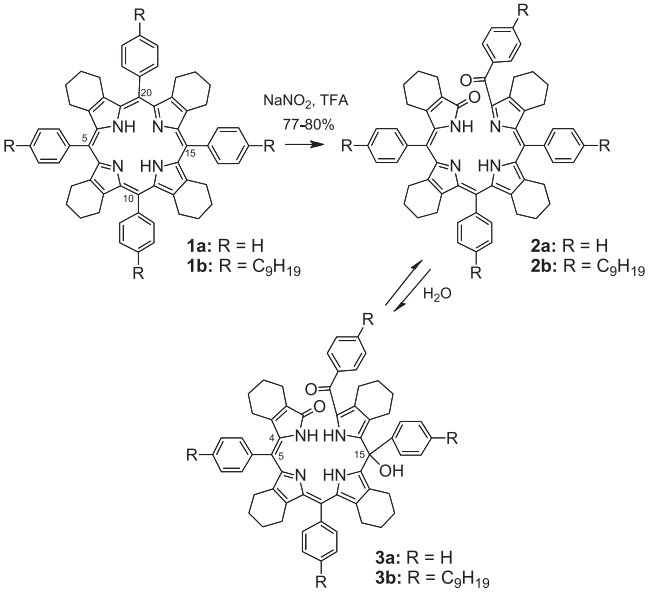
undergoes nucleophilic addition of water to produce the corresponding hydrated biliverdin.

The 300 MHz ^{1}H NMR spectra of benzoylbiliverdins **3a**[24] showed the asymmetry of both tetrapyrroles, i.e., three N–H signals and one O–H signal that appeared at 11.5, 11.2, 9.0, and 6.0 ppm, respectively, all of these ^{1}H NMR absorptions disappeared upon performing a deuterium oxide shake on the tetrapyrrole that was purple in color. The ^{13}C spectrum of **3a** showed a benzoyl carbonyl peak at 187 ppm, the lactam carbonyl at 174 ppm and a quaternary carbon peak at 75 ppm. The tetrapyrrole that was pink in color, on the other hand, gave a ^{1}H NMR spectrum with two N–H peaks appearing at 12.5 and 9.46, two distinct singlets, one of them corresponding to the hydroxyl group, appeared at 4.1 and 3.7 ppm. A deuterium oxide shake resulted to the disappearance of the two N–H protons and one of the singlet peaks that had previously appeared at 4.1 ppm. The ^{13}C spectrum of the pink tetrapyrrole[24] differed only slightly from that of the purple tetrapyrrole with very similar carbonyl frequencies appearing at 187 and 172.4 ppm, along with a quaternary carbon peak at 77.7 ppm. Characteristic benzoylbiliverdin fragments were obtained by high resolution EIMS for both chromophores; these had M+Na ion peaks at *m*/*z* 903.4249 and 903.4224 for the pink and purple tetrapyrroles, respectively. Oxidations were also carried out using anhydrous methanol, ethanol, and methylamine to quench the reactions, and while methylamine gave no addition product at all, the methanol and ethanol adducts were formed in almost negligible amounts as inferred from the appearance of near-baseline *m*/*z* 913 and 927 peaks. Both steric and electronic (such as, solvents being less nucleophilic than H_2O) effects may be invoked to account for the above observations. Unfortunately, the amounts of the above products obtained were too small for any further analyses to be performed.



Biliverdins usually adopt an helical all-*syn* conformation due to an efficient intrachromophoric hydrogen bond system based on the N–H···N–H network. Studies carried out on biliverdin IXα esters have shown the $\varepsilon_{(vis)}/\varepsilon_{(UV)}$ ratio to be a function of the verdin molecular extension. An increase in ratio indicates a change in the porphyrin-like helically coiled form (5Z, 10Z, 15Z) to a more extended form, (e.g., 5Z, 10E, 15Z or 5E, 10Z, 15Z), where the ratio is similar to that of a polyene.[30–32] In our study, the $\varepsilon_{(vis)}/\varepsilon_{(UV)}$ of the purple and pink biliverdin conformers was 0.47 and 0.64, respectively, indicating a more stretched conformation for the pink conformer than the purple one. All free biliverdins normally tend to adopt the ZZZ helicoidal conformation with an $\varepsilon_{(vis)}/\varepsilon_{(UV)}$ ratio of 0.25 in agreement with molecular orbital calculations.[33–37] Helicoidal (ZZZ)–biliverdins could be photoisomerized to their extended EZZ or EZE conformers but the latter reconverted back to the helical forms.[38] This explains the ~3:1 isolation of the violet biliverdin **3a** versus the more polar pink conformer of **3a**.

When porphyrin **1b** was oxidized under similar conditions to those for **1a**, only bilatrienone **2b** and biladienone **3b** were obtained, in 70 and 15% yields, respectively, with no traces of the pink conformer of **3b**. This could be a result of the alkyl substituent on the phenyl ring, which does not favor the EZ isomerization of the C4–C5 bond; similar results were reported for etiobiliverdin by Mizutani et al. who reported that the energy difference between the ZZZ and EZZ isomers is ascribed to the steric repulsion between the β-alkyl groups and the pyrrole ring.[39] We believe that the sole product of the chemical oxidation of porphyrin **1b** is bilatrienone **2b** along with some traces of starting material. However upon workup and chromatographic purification, biladienone **3b** is isolated after addition of a water molecule across the methine carbon bridge. This could be further argued with the fact that upon subjecting **3b** to higher temperatures e.g., 40 °C, compound **2b** was isolated, as confirmed by TLC, UV–vis and ^{1}H NMR spectroscopy.

A final confirmation of the molecular structure of biliverdin **2b** and the purple benzoylbiliverdin **3a** was provided by X-ray crystallography. Figure 1 shows the X-ray structure of benzoylbiliverdin **2b**, with arbitrarily small C atoms for the *n*-nonyl groups. The central part of the molecule has a helical shape. Internal N–H···N hydrogen bonds allow each C(pyrrole)$_2$ group to be reasonably planar, with mean deviations of 0.06 and 0.11 Å for these 11-atom fragments. However, these two planes form a dihedral angle of 29.3(2)° due to the helical twist of the acyclic molecule, which also brings phenyl groups of (C_9H_{19})Ph substituents at opposite ends of the molecule into edge-to-face contact. Parameters of this interaction are C···centroid distance 3.456 Å and C–H···centroid angle 147°. Two of the nonyl groups are extended, while the other two are quite tortuous, as shown schematically in Figure 1.

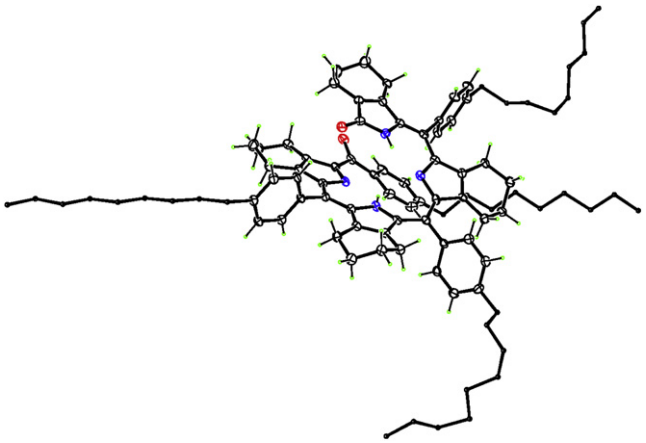


Figure 1. ORTEP diagram showing the molecular structure of **2b**.

An examination of the X-ray structure of biliverdin **3a** (obtained by slow diffusion of hexane into a solution of chloroform) shows the compound to be a biladienone, with the third *meso*-carbon (C15) a tetra-substituted one and bearing a hydroxyl group (see Fig. 2). The existence of the –OH group is thus unequivocally established and corroborates the structural conclusions reached from ^{13}C NMR data, which showed the presence of a quaternary *meso*- carbon at δ 75 ppm. Within a single crystal, two molecules of the biliverdin associate with each other to form intermolecularly hydrogen-bonded pairs (Fig. 3). Triads of hydrogen bonds exist

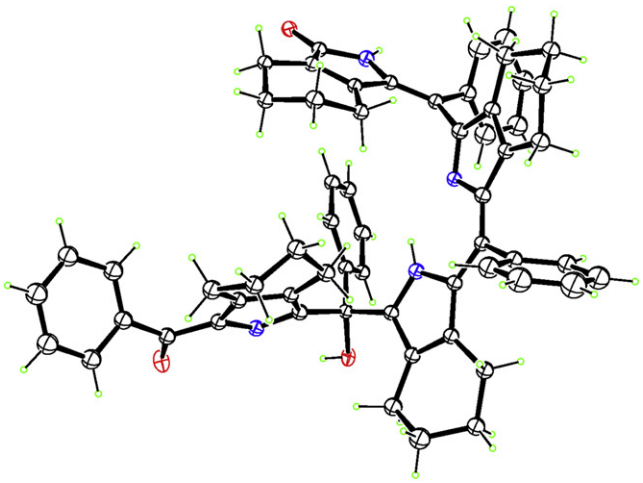


Figure 2. ORTEP diagram showing the molecular structure of **3a**.

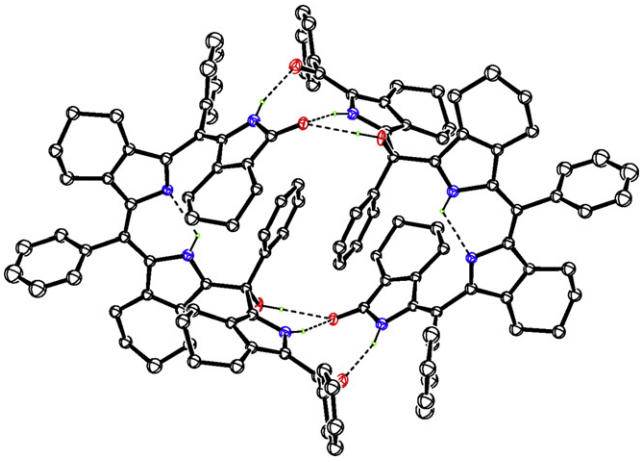


Figure 3. ORTEP diagram of **3a** pair showing hydrogen bonding.

about an inversion center, with the participating groups being the lactam unit on one molecule and the benzoyl carbonyl, the pyrrole –NH, and most importantly, the *meso*-OH on the other. The *meso*-OH•••O (1) bond, though slightly extended, lies at a nearly perfect hydrogen bonding angle of ~179° thus allowing for moderately strong hydrogen bonds; the remaining hydrogen bonds lie within 20% of the optimum angle of 180°. Stabilization offered by the intermolecular association may be the *raison d'etre* for the hydroxyl group and may explain the readiness of the initially-formed bilatrienone **2a** to add a molecule of water across one of its double bonds to give the above biliverdin. The same, along with steric factors, may also explain why oxidations performed in methanol, ethanol, or methylamine media almost completely failed to give the corresponding addition products or gave so only in negligible quantities.

One consequence of the hydrogen bonding is that it predisposes the C4–C5 double bond into an *E*- configuration, making the (*EZ*)-biladienone arrangement the most stable one for this biliverdin. This, however, does not discount the possibility of various other arrangements that may arise out of bond-rotation about the above double bond. Our theoretical calculations (B3LYP/6-31G*) do in fact predict the existence of various stereoisomers of the biladienone, which differ in energies by 6–10 Kcal/mol at room temperature, and may explain why this compound is obtained as two different colored forms-namely the violet and the pink. In fact, similar isomeric biladienones were obtained by Mizutani et al., although from a metallo-TPP, and under oxidation conditions different than those reported herein.[29]

3. Experimental

3.1. General

Silica gel 60 (70–230 and 230–400 mesh, Merck) or neutral alumina (Merck; usually Brockmann Grade III) was used for column chromatography. Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 silica gel (pre-coated sheets, 0.2 mm thick). Reactions were monitored by TLC and spectrophotometry. ^{1}H NMR spectra were obtained in deuterochloroform or acetone-d_6 solution, using a Bruker 250 or 400 MHz spectrometer; chemical shifts are expressed in ppm relative to residual chloroform (7.26 ppm) or internal TMS (0 ppm). Unless otherwise stated, electronic absorption spectra were measured in dichloromethane solution using a Hewlett-Packard 8450A spectrophotometer. Mass spectra were obtained at the Mass Spectrometry Facility at Louisiana State University. Benzaldehyde, $BF_3{\cdot}OEt_2$, dichloro-dicyanobenzoquinone (DDQ) were used as purchased. All solvents were dried and purified according to literature procedures.

*3.1.1. 5,10,15,20-Tetra(4-nonanylphenyl)-2:3,7:8,12:13,17:18-tetrabutanoporphyrin (**1b**).* The compound (**1b**) was prepared from the condensation of 3:4-butanopyrrole (0.25 g, 2.14 mmol) with 4-nonanyl-benzaldehyde (0.5 g, 2.14 mmol), in freshly distilled and dry dichloromethane (214 mL) and in the presence of $BF_3{\cdot}OEt_2$ (0.04 mL, 0.214 mmol), under argon. The reaction mixture was stirred for 1 h at room temperature, after which DDQ (0.7 g, 3.21 mmol) was added and the final mixture was refluxed under argon for 1 h to give a dark green solution. The solvent was reduced to dryness under vacuum and the resulting residue purified by alumina column chromatography using 2% methanol in dichloromethane for elution. Recrystallization from hot methanol gave purple crystals of the title porphyrin (0.5 g, 70% yield), mp>300 °C. ^{1}H NMR ($CDCl_3$, drop of d-TFA), δ (ppm), 8.10 (d, 8H, J=7.7 Hz) 7.91 (d, 8H, J=7.8 Hz), 2.97–2.92 (t, 8H, J=7.6 Hz), 2.33, (br s, 8H), 1.95–1.29 (m, 80H), 0.94–0.92 (t, 12H, J=7.2 Hz). ^{13}C NMR ($CDCl_3$) 144.1, 140.7, 136.2, 129.1, 118.5, 37.4, 33.5, 33.1, 31.29, 31.24, 30.97, 30.64, 27.3, 25.1, 24.2, 15.7. UV–vis (CH_2Cl_2) λ_{max} 446 nm (ε 66,100), 542 nm (5100), 615 nm (3700), 679 nm (55 700), MS (MALDI) m/z 1335.30 (M^+). Anal. Calcd for $C_{96}H_{126}N_4$: C, 84.03; H, 9.56; N, 4.09. Found: C, 84.23; H, 9.35; N, 4.24. The 4-nonanyl-benzaldehyde was obtained from the reaction of 1-octylbromide (50 mM, 10.8 g) in diethyl ether (50 mL) and under argon with magnesium turnings (10 g) at room temperature. After stirring for 30 min the reaction mixture was cooled to 0 °C and bromobenzaldehyde (40 mM, 6.75 g) was slowly added. The final mixture was allowed to stir for 1 h and then quenched and washed with water (2×50 mL) and dried over Na_2SO_4. The organic solvents were evaporated under vacuum and the resulting yellow oil was taken up in hexane and purified by silica gel chromatography, using 3:1 hexane and ethyl acetate solution for elution. 1-(4-Bromophenyl)-1-hydroxynonane was obtained in 14.6 g (97% yield); ^{1}H NMR ($CDCl_3$,), δ (ppm), 7.45 (d, 2H, J=8.4 Hz), 7.20 (d, 2H, J=7.8 Hz), 4.61 (s, broad, 1H), 1.98 (s, 1H) 1.9–1.2 (m, 14H), 0.85 (t, 3H, J=6.8 Hz). MS (FAB) m/z 299.17 (M^+). To a solution of 1-(4-bromophenyl)-1-hydroxynonane (50 mM, 14.9 g) in 150 mL of acetonitrile, (300 mM, 27 mL) of trimethylsilylchloride (TMSC) and (300 mM, 45 g) of sodium iodide were added and the final mixture was stirred under argon for 12 h at room temperature. The reaction mixture was washed with an aqueous solution of $Na_2S_2O_3$, dried over Na_2SO_4 and the organic solvent evaporated under reduced

pressure affording an orange oil. The orange oil was diluted with 150 mL of DMSO and (750 mM, 2.85 g) of $NaBH_4$ was slowly added. The resulting solution was stirred under argon for 12 h and then extracted into hexane and purified by silica gel chromatography using hexane for elution. The first band collected was 4-bromophenylnonane (10.7 g, 76.3%). ^{1}H NMR ($CDCl_3$), δ (ppm), 7.42 (d, 2H, J=8.4 Hz), 7.08 (d, 2H, J=7.8 Hz), 2.60 (t, 2H, J=7.6 Hz) 1.58–1.29 (m, 14H), 0.91 (t, 3H, J=7.2 Hz). MS (FAB) m/z 282.16 (M^+). 4-Bromophenylnonane (15 mM, 4.25 g) was dissolved in freshly distilled THF (50 mL) and the reaction mixture cooled to −78 °C. *n*-BuLi (46 mM, 26.5 mL) was then added dropwise and the mixture was stirred at −78 °C for 1 h. Dry DMF (46 mM, 3.0 mL) was then added dropwise and the final mixture stirred under argon for 1 h. The reaction mixture was allowed to warm up to room temperature and then quenched with 100 mL of 1 M HCl. The mixture was extracted into hexanes (3×100 mL), washed with water (2×100 mL), dried over Na_2SO_4 and the solvent removed under reduced pressure to give a yellow oil. 4-Nonanylbenzaldehyde was purified by silica gel chromatography using a 3:1 solution of hexane/ethyl acetate for elution to give an oil (2.3 g, 65% yield). ^{1}H NMR ($CDCl_3$), δ (ppm), 10.0 (s, 1H), 7.82 (d, 2H, J=8.4 Hz), 7.36 (d, 2H, J=7.8 Hz), 2.74 (m, 2H) 1.69–1.29 (m, 14H), 0.93 (t, 3H, J=7.2 Hz). MS (FAB) m/z 233.26 (M^+).

*3.1.2. Benzoylbiliverdins **2a** and **3a**.* The compounds **2a** and **3a** were prepared and characterized as we have previously described.[24]

*3.1.3. Benzoylbiliverdins **2b** and **3b**.* Porphyrin **1b** (100 mg, 0.074 mmol) was dissolved in 2 mL of TFA and $NaNO_2$ (30 mg, 0.45 mM) was added to the solution while stirring under air at room temperature for 3 min. The reaction was quenched by pouring into 50 mL of water, followed by extraction with dichloromethane (6×25 mL). The organic layers were washed with saturated aqueous $NaHCO_3$ (2×100 mL), then with water (100 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the resulting residue was taken up in chloroform and purified by alumina column chromatography using a gradient elution of chloroform to 1% methanol in chloroform. The title biliverdin **2b** was the first green band eluted using pure chloroform (71 mg, 70%). The benzoylbiliverdin **3b** (violet color) was eluted next using 1% methanol in chloroform solution (15 mg, 15%) yield. For the title biliverdin **2b**: mp=245–247 °C. UV–vis (CH_2Cl_2) λ_{max} 332 nm (ε 30,600), 447 (31,600), 683 (7800). MS (MALDI-TOF) m/z 1368.3 (M^+). ^{1}H NMR ($CDCl_3$), δ (ppm), 12.80 (br s, 1H), 10.80 (br s, 1H), 8.22–6.75 (m, 16H), 2.76–1.33 (m, 96H), 0.94 (m, 12H): Anal. Calcd for $C_{96}H_{126}N_4O_2$: C, 80.05; H, 9.38; N 3.89. Found: C, 80.07; H, 9.07; N, 3.83. For biliverdin **3b**: mp=185–190 °C; UV–vis (CH_2Cl_2) λ_{max} 345 nm (ε 47 100), 576 nm (22 700). MS (MALDI-TOF) m/z 1386.4 (M^+). ^{1}H NMR ($CDCl_3$), δ (ppm), 11.52, 11.45 (2 br s, 2H), 8.86 (s, 1H), 7.56 (d, J=8.0 Hz, 2H), 7.40 (d, J=8.0 Hz, 2H), 7.3–7.1 (m, 12H), 6.10 (s, 1H), 2.7–1.24 (m, 96H), 0.94 (br s, 12H). ^{13}C NMR ($CDCl_3$), δ (ppm), 172.2, 163.5, 146.6, 145.3, 144.3, 143.5, 143.2, 139.6, 138.8, 137.7, 136.6, 135.6, 135.1, 134.2, 133.5, 131.1, 129.8, 128.9, 128.5, 128.3, 127.2, 125.3, 120.6, 119.4, 74.1, 36.1, 35.8, 35.7, 32.1, 31.8, 31.6, 29.8, 29.7, 29.6, 29.5, 29.1, 24.9, 24.1, 23.4, 23.0, 22.9. Anal. Calcd for $C_{96}H_{128}N_4O_3$: C, 83.19; H, 9.31; N, 4.04. Found: C, 82.98; H, 9.24; N, 4.12.

3.1.4. Crystal molecular structures. Bilatrienone **2b**, $C_{96}H_{126}N_4O_2\cdot H_2O\cdot MeOH$, M_r=1418.1, triclinic, space group P-1, a=14.222(5), b=16.640(6), c=19.510(10) Å, α=92.097(14), β=103.467(15), γ=107.381(19)°, V=4257(3) Å^3, Z=2, Mo-$K\alpha$ radiation (λ=0.71073 Å; μ=0.066 mm^{-1}), T=110 K, 22 253 data by Nonius Kappa CCD, R=0.122 ($F^2>2\sigma$), for 11 688 unique data having θ_{max}=23.0° and 906 refined parameters. Displacement parameters are large for three of the nonanyl groups, and anisotropic refinement of one of them was not possible. Solvent H atoms were not located. CCDC 745873, available from the Cambridge Crystallographic Data Centre.

Biladienone **3a**, $C_{60}H_{56}N_4O_3\cdot CH_2Cl_2$, M_r=966.01, triclinic, space group P-1, a=12.483(10), b=13.993(12), c=16.320(17) Å, α=75.65(3), β=75.83(3), γ=67.91(6)°, V=2522(4) Å^3, Z=2, Mo-$K\alpha$ radiation (λ=0.71073 Å; μ=0.180 mm^{-1}), T=110 K, 26 049 data by Nonius Kappa CCD, R=0.151 ($F^2>2\sigma$) for 6470 unique data having θ_{max}=23.1° and 306 refined parameters. As a result of the small number (1771) of unique intensities having $I>2\sigma(I)$, only O and solvent Cl atoms were refined anisotropically. CCDC 745874, available from the Cambridge Crystallographic Data Centre.

4. Conclusions

It is shown that bilitrienones **2** are obtained from oxidation of metal-free dodecasubstituted porphyrins **1** in the presence of sodium nitrite, trifluoroacetic acid and air oxygen. Bilitrienone **2b** is obtained from the 5,10,15,20-tetra(*p*-nonanylphenyl)porphyrin **1b**, this being the first example of the unmodified metal-free open-chain tetrapyrrole to be reported; the structure of **2b** is characterized by X-ray crystallography. In the absence of the *para*-nonanyl groups the initially-formed bilitrienone **2a** undergoes a rapid and spontaneous hydration reaction to give biladienone **3a** as the major isolated product. The molecular structure of **3a** is also presented.

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