Benzoylbiliverdins from chemical oxidation of dodeca-substituted porphyrins†

Owendi Ongayi, Frank R. Fronczek and M. Graça H. Vicente*

*Department of Chemistry, Louisiana State University, Baton Rouge, LA 70803, USA*

Oxidation of dodeca-substituted porphyrin 1 in the presence of NaNO₂/TFA and air afforded benzoylbiliverdin 3 in 77% yield; under similar conditions the Ni(II)-porphyrin 2 was mainly nitrated at a cyclohexenyl ring; key X-ray structures are presented.

Metallo-porphyrins are traditionally photooxidized to give the corresponding metallo-formylbiliverdins,[1] which can be further degraded to produce bilirubins and, ultimately, maleimides and succinimides. This reaction mimics the major biochemical processes of heme catabolism and chlorophyll degradation.[1,2] On the other hand, metallo-*meso*-tetraarylporphyrins, such as 5,10,15,20-tetraphenylporphyrin (TPP), can be oxidized to benzoylbiliverdins by chemical oxidation using cerium(IV) or thallium(III) salts,[3] by reactions of metalloporphyrin π-cation radical with nucleophiles,[4] and by photooxygenation.[5,6] In general, the yields reported for the benzoylbiliverdin of TPP using these procedures are low. Herein we report the ready preparation of a stable benzoylbiliverdin from a metal-free dodeca-substituted porphyrin 1, in 77% yield, and of its Ni(II) and Cu(II) metal complexes.

Porphyrin 1 was found to be readily oxidized in the presence of NaNO₂ and trifluoroacetic acid (TFA). Under these conditions TPP is regioselectively nitrated at the *p*-positions of the *meso*-phenyl rings.[7] However, due to the steric hindrance caused by the peripheral substituents of 1,[8] this porphyrin is easier to oxidize than TPP under these conditions, and reacts so as to relieve steric strain. Other examples of the unusual reactivity of non-planar porphyrin macrocyles are reported in the literature.[9,10]

When 6 equiv. of NaNO₂ were added to a concentrated green solution of 1[11] (45 mg) in TFA (3 mL) under air, the color of the solution immediately changed to brown. After stirring for 10 minutes under air at room temperature, the reaction mixture was quenched with water and neutralized. The major purple product isolated, in 77% yield, was benzoylbiliverdin 3, along with 6% recovered starting material 1 and trace amounts of polynitrated products. When the same reaction was performed under an inert atmosphere of argon, or in the absence of TFA using CH₂Cl₂ as solvent, only starting material 1 was recovered. No spectroscopic evidence was found during the reaction for the involvement of an isoporphyrin intermediate, and a radical scavenger (2,6-di-*tert*-butyl-4-methylphenol) added to the reaction mixture completely inhibited the formation of benzoylbiliverdin 3. These results indicate that the mechanism of the reaction may involve oxidation of the porphyrin macrocycle to the corresponding π-cation radical by NO⁺,[9,12] followed by reaction with air oxygen and ring opening. No benzoylbiliverdin 3 was detected when porphyrin 1 or its Zn(II) or Ni(II) complexes were stirred under normal laboratory fluorescent light and a stream of air for up to 48 h. Metal insertion into 3 using Ni(II) or Cu(II) acetate in refluxing toluene under argon gave the metal complexes 4 and 5, in quantitative and 80% yields, respectively. Unlike previously reported metallo-bili-

verdins, 4 and 5 were found to be highly stable to air, mildly acidic and basic conditions, and highly soluble in organic solvents.

1: M = 2H
2: M = Ni(II)

3: M = 2H
4: M = Ni(II)
5: M = Cu(II)
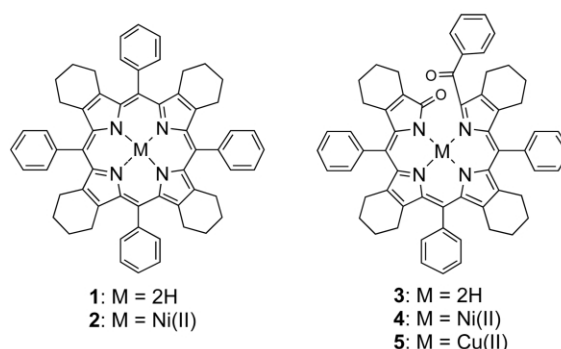
The molecular structure‡ of Ni(II)-biliverdin 4 is given in Fig. 1. The oxidized, nonmacrocyclic nature of the ligand forces distortions from square-planar coordination of the Ni(II) center. The N atoms at the oxidized ends of the ligand lie 0.65(1) and −0.68(1) Å out of the plane defined by the Ni and the two central N atoms. Ni–N distances fall within the range 1.835(8)–1.884(7) Å. The benzoyl O atom forms a longer intramolecular distance of 2.882(7) Å to the Ni atom.

The UV-Vis of benzoylbiliverdins 3–5 are given in Fig. 2. Typically, porphyrin macrocycles, such as 1 and 2, display strong absorptions in the visible region of the spectrum, namely a Soret band between 390–440 nm and less intense Q bands between 500–680 nm. Oxidation and opening of the porphyrin macrocycle cause the disappearance of these bands in agreement with literature reports on the biliverdin of TPP.[3,5] In contrast, the Ni(II) and Cu(II) complexes 4 and 5 display strong absorptions in the visible and near-IR regions (Fig. 2) possibly as a result of their cyclic conformation. In addition, the
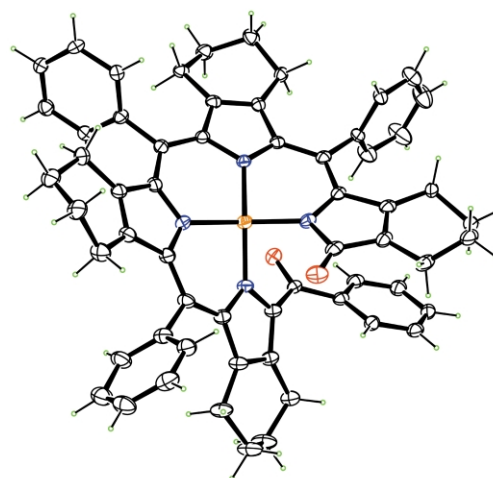

Fig. 1 Molecular structure of Ni(II)-benzoylbiliverdin 4.

† Electronic supplementary information (ESI) available: selected data for 3–6; scheme showing the formation of 6 and 7 from Ni(II)-porphyrin 2. See http://www.rsc.org/suppdata/cc/b3/b306586c/

fluorescence spectrum of diamagnetic complex **4** shows a single emission band at 895 nm upon excitation at 438 nm, in CHCl₃, which indicates that such compounds can potentially be developed as near-IR fluorescent markers.

Under similar conditions, albeit in the presence of a catalytic amount of TFA to prevent immediate demetalation, the Ni(II)-porphyrin **2** was mainly nitrated[13] at a cyclohexenyl ring, presumably because NO⁺ is not formed in significant amount under these conditions. When a mixture of Ni(II) complex **2** and 1.5 equiv. of NaNO₂ in 1% TFA/toluene was stirred at room temperature under air for 12 hours, the benzoylbiliverdin **4** was obtained in only 10% yield. The major product of this reaction was nitro-cyclohexadienylporphyrin **6**, in 40% yield, and recovered starting material **2**, in 30% yield. When the reaction was heated to 50 °C overnight, the major product obtained was the regioisomer nitro-cyclohexadienylporphyrin **7**, in 40% yield. This compound could also be prepared quantitatively from **6**, by acid catalyzed isomerization, in 1% TFA/toluene. This double bond isomerization allows the 2′ sp² carbon to move away from the adjacent *meso*-phenyl ring by becoming sp³ hybridized, which decreases steric hindrance. Under the above reaction conditions, the Ni(II)-porphyrin **2** is probably initially oxidized to the corresponding cyclohexenylporphyrin and subsequently nitrated at the double bond to produce **6**, followed by acid catalyzed isomerization to give **7**. A similar nitration of the vinyl groups of protoporphyrin-IX dimethyl ester has been previously reported.[12]

Nitrated porphyrins **6** and **7** are characterized by a M⁺ peak at m/z 929.1 in their MS (ESI), and the aborption bands of **6** in the UV-Vis spectrum are red-shifted by 12 nm compared with those of **7**. The molecular structure‡ of Ni(II) complex **7** is given in Fig. 3. Coordination of the Ni(II) center is square planar with a slight tetrahedral distortion. N atoms lie alternately ±0.16(1) Å from the N₄Ni best plane, in which the Ni lies. Ni–N distances range 1.905(9)–1.920(8) Å. The molecule has an overall saddle shape. The NO₂ group is occupationally disordered on two rings, being present 60(1)% of the time in the position shown, and 40(1)% of the time (not shown) in the position related by a 90° clockwise rotation in Fig. 3. The C atoms shown with open circles in both rings are also disordered, as the ring is unsaturated when the NO₂ is present.

In summary, we have synthesized novel undeca-substituted benzoylbiliverdins by mild oxidation, in the presence of air and NaNO₂/TFA, of metal-free dodeca-substituted porphyrin **1**. The Ni(II) and Cu(II) complexes of the benzoylbiliverdin show intense absorption bands in the visible and near-IR, and the Ni(II) complex **4** displays a fluorescence band in the IR region. Nitro-cyclohexadienylporphyrins **6** and **7** were the major products obtained under similar conditions but using only a catalytic amount of TFA, from Ni(II)-porphyrin **2**.
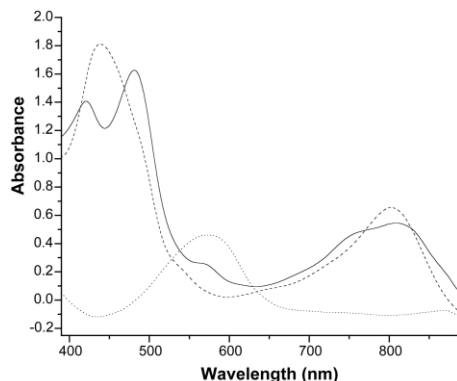
Fig. 2 Comparison of the absorption spectra (in CH₂Cl₂) of benzoylbili-verdins **3** (···), **4** (---) and **5** (—).

1: M = 2H
2: M = Ni(II)

3: M = 2H
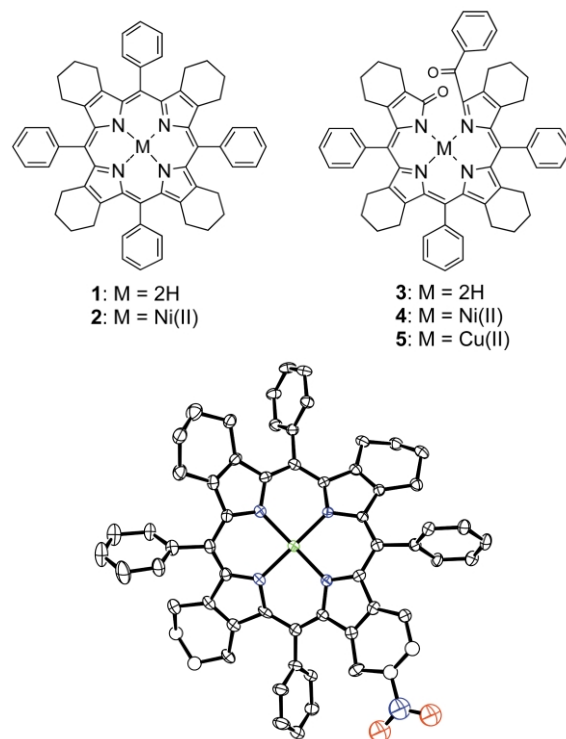**4**: M = Ni(II)
5: M = Cu(II)

Fig. 3 Molecular structure of **7**. The NO₂ group and two six-membered rings are disordered (see text).

Notes and references

‡ Ni(II) benzoylbiliverdin **4**, C₆₀H₅₂N₄NiO₂·CH₂Cl₂·MeOH·0.5H₂O, M_r = 1045.7, monoclinic, space group $P2_1/c$, a = 18.426(13), b = 13.713(13), c = 23.955(19) Å, β = 101.90(4)°, V = 5923(8) Å³, Z = 4, ρ_{calc} = 1.173 g cm⁻³, Mo-Kα radiation (λ = 0.71073 Å; μ = 0.464 mm⁻¹), T = 100 K, 28976 data by Nonius KappaCCD, R = 0.130 ($F^2 > 2\sigma$), Rw = 0.370 (all F^2) for 7610 unique data having θ < 23.3° and 684 refined parameters. There is considerable disorder involving the MeOH and water solvent molecules. Ni(II) nitrocyclohexylporphyrin **7**, C₆₀H₄₉N₅NiO₂·0.5H₂O, M_r = 939.8, monoclinic, space group $P2_1/c$, a = 16.369(7), b = 23.960(9), c = 13.461(5) Å, β = 101.39(2)°, V = 5176(4) Å³, Z = 4, ρ_{calc} = 1.206 g cm⁻³, Mo-Kα radiation (λ = 0.71073 Å; μ = 0.423 mm⁻¹), T = 100 K, 25395 data by Nonius KappaCCD, R = 0.112 ($F^2 > 2\sigma$), Rw = 0.341 (all F^2) for 6891 unique data having θ < 22.5° and 594 refined parameters. CCDC 211040 (**4**) and 211039 (**7**). See http://www.rsc.org/suppdata/cc/b3/b306586c/ for crystallographic data in CIF or other electronic format.

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