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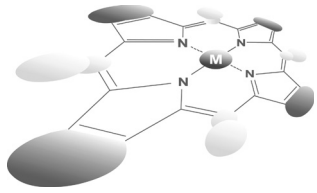

Substituent effects on selectivity of coupled oxidation of iron tetraphenylporphyrins

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ABSTRACT: Coupled oxidation of iron tetraphenylporphyrins bearing either a OMe, Me, F, Cl, COOMe, CF_3 or CN group in the *para*-position of the phenyl groups gave tetraarylbiladien-*ab*-1-one and triarylbilindione. The ratios of the yields of the former to those of the latter were linearly correlated with the Hammett substituent constants σ_p^+, with a positive slope ($\Delta\rho = 0.64$). The Hammett plot of the oxidation rate *vs.* the substituent constant σ_p also showed a positive slope ($\rho = 0.30$). These substituent effects suggest that a nucleophilic step is included in the formation of bilindione. Coupled oxidation of an A3B type tetraarylporphyrin having an electron withdrawing nitro group in one of the phenyl groups indicated that the oxidation leading to biladienone occurred rather statistically in any of the *meso*-positions, while the oxidation leading to bilindione occurred preferentially in the *meso*-position bearing the 4-nitrophenyl group.

KEYWORDS: oxidation, porphyrinoids, substituent effects, iron, linear tetrapyrrole.

INTRODUCTION

Oxidative ring opening reactions of porphyrins or its analogues are important as catabolism of cyclic tetrapyrroles and biosynthesis of linear tetrapyrroles in nature. Bilindione [1] (biliverdin) is a linear tetrapyrrole and biosynthesized from iron porphyrin (heme) by a reaction catalyzed by heme oxygenase [2]. The red chlorophyll catabolite is also a linear tetrapyrrole [3]. Oxidation of free base chlorin (pheophorbide *a*) is catalysed by pheophorbide *a* oxygenase [4]. As a model reaction of biological oxidation of cyclic tetrapyrroles, coupled oxidation of iron porphyrins with substituents in the pyrrole β-positions but none in the *meso*-positions was studied in detail by Lemberg and others [5]. Compared to the regioselective oxidation by enzymes, coupled oxidation of unsymmetrically substituted porphyrins usually occurs non-selectively at *meso*-positions. Previously we reported that electronic effects of a CF_3 group on the pyrrole β-position of iron porphyrin directed the oxidation site to the most electron-rich *meso*-position [6].

The oxidation of [tetraarylporphyrinato]iron(III) chloride carrying phenyl groups at the *meso*-positions with molecular dioxygen in the presence of ascorbic acid and pyridine gave biladien-*ab*-1-one [7–9] as the major product and bilindione as a minor one [8,10]. Biladien-*ab*-1-one has been obtained by various reactions such as photochemical oxidation of tetraarylporphyrins, while *meso*-arylbilindione was prepared only by the coupled oxidation [8]. Therefore, it would be desirable to improve the selectivity of bilindione in the coupled oxidation.

We previously reported that the lactam and carbonyl oxygens in biladien-*ab*-1-one were derived from one dioxygen molecule, while the two lactam oxygens in bilindione were derived from two dioxygen molecules based on the isotope labeling studies using $^{18}O_2$ [11]. We proposed that a possible key intermediate in the coupled oxidation of tetraarylporphyrin was the 19-benzoylbilinone iron complex [11]. However, details of the reaction mechanism and how the electronic effects

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control the bilindione/biladienone selectivity as well as the *meso* selectivity for unsymmetrically substituted tetraarylporphyrins are still unknown.

In this paper, we studied coupled oxidation of a series of tetraarylporphyrins bearing substituent(s) in the *para*-position to clarify electronic effects of the substituents on the reaction selectivity. We also investigated coupled oxidation of the iron complex of 5-(4-nitrophenyl)-10,15,20-triphenylporphyrin. Hammett analysis of the selectivity of the coupled oxidation as well as the selectivity of coupled oxidation of A3B type tetraarylporphyrins suggested that an electron withdrawing group in the phenyl group would facilitate the oxidative cleavage of the phenyl group to afford bilindione. We demonstrated that coupled oxidation can be applied to a number of tetraarylporphyrins bearing various substituents such as alkoxy, alkyl, ester, cyano, and halogens.

RESULTS AND DISCUSSION

Substituent effects on bilindione/biladienone selectivity of coupled oxidation

Meso-tetraphenylporphyrins (TPPs) having various substituents in the *para*-position were synthesized and their iron complexes were prepared by refluxing them with $FeCl_2$ in DMF. Reaction of the iron porphyrins with dioxygen, ascorbic acid, and pyridine, followed by work up with hydrochloric acid gave biladien-*ab*-1-ones and bilindiones (see Scheme 1). The isolated yields of biladien-*ab*-1-ones and bilindiones are listed in Table 1.

Previously we reported that there was a tendency that the yields of biladien-*ab*-1-one **2** increased as the substituents on the aryl groups were electron-donating, while the yields of bilindiones **3** increased as the substituents were electron-withdrawing [10]. To analyze the substituent effects, we plot the ratios of the yields of bilindione **3** to those of biladien-*ab*-1-one **2**, Y_r, against Hammett substituent constants σ_p^+ [12] in Fig. 1. We found that log Y_r was linearly correlated with σ_p^+ and the slope of the line was 0.64.

When the rate constant of formation of **2**, that of formation of **3**, and that of side reactions are assumed to be k_1, k_2 and k_3, respectively, then the yields of **2** and **3** can be given by:

$$[\mathbf{2}] = \frac{k_1}{k_1 + k_2 + k_3}\left(1 - [\mathbf{1}]_0 e^{-(k_1+k_2+k_3)t}\right) \rightarrow \frac{k_1}{k_1 + k_2 + k_3}(t \rightarrow \infty) \quad (1)$$

$$[\mathbf{3}] = \frac{k_2}{k_1 + k_2 + k_3}\left(1 - [\mathbf{1}]_0 e^{-(k_1+k_2+k_3)t}\right) \rightarrow \frac{k_2}{k_1 + k_2 + k_3}(t \rightarrow \infty) \quad (2)$$

If these rate constants follow the Hammett equation: log $k_1 = \rho_1\sigma_p^+$ and log $k_2 = \rho_2\sigma_p^+$, then Y_r is given by:

$$\log Y_r = \log k_2 - \log k_1 = \Delta\rho\sigma_p^+ \text{ where} \quad (3)$$

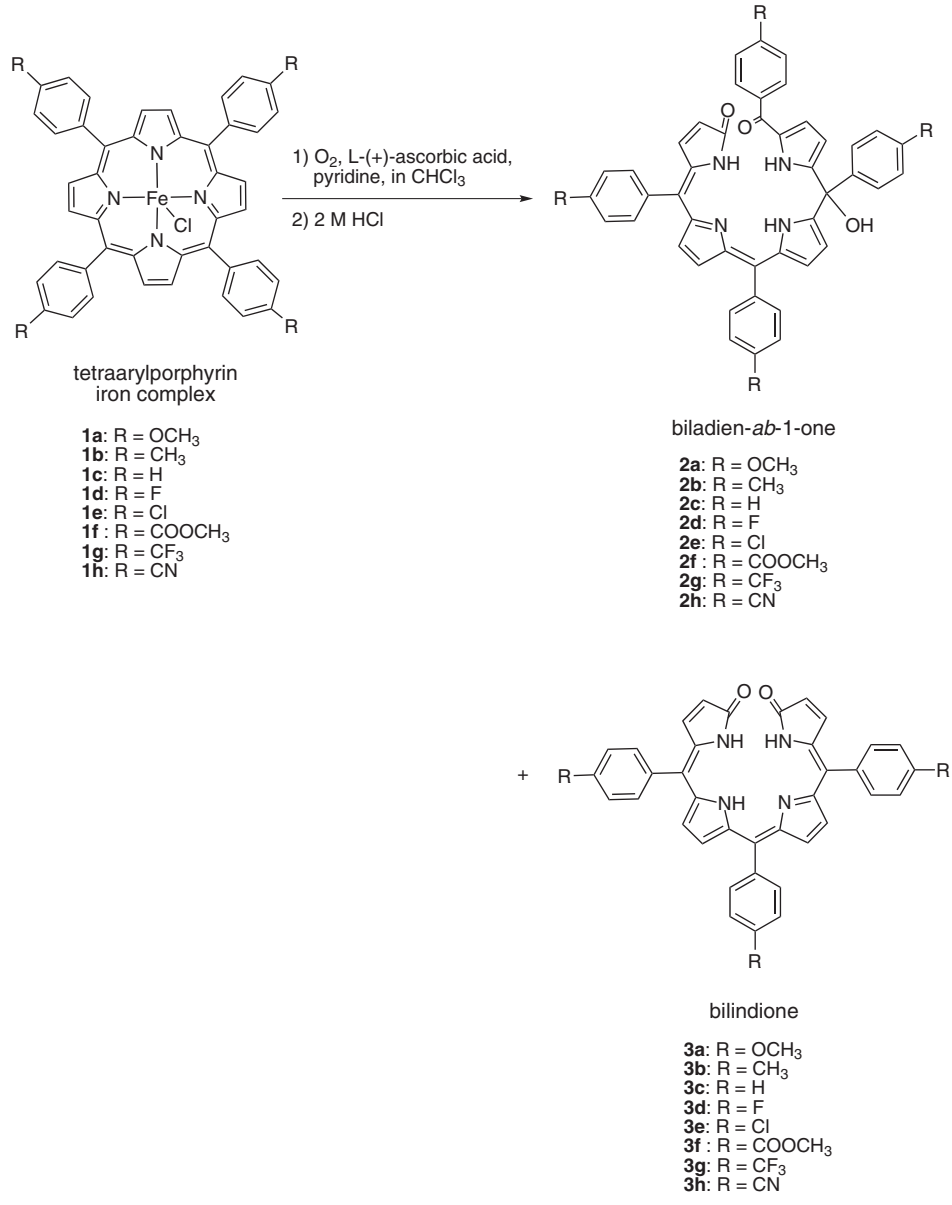
$$\Delta\rho = \rho_2 - \rho_1. \quad (4)$$

Therefore the slope of the line shown in Fig. 1 is $\Delta\rho$, the difference in the reaction constant of bilindione formation and that of biladienone formation; $\Delta\rho = 0.64 \pm 0.04$. The correlation coefficient r^2 was 0.968. If a common intermediate such as a 19-benzoylbilinone iron complex was assumed, $\Delta\rho$ should be interpreted as the difference in the reaction constants from the intermediate. When the Hammett substituent constants σ_p [13] were used instead of σ_p^+, poorer linear correlation was observed: $r^2 = 0.915$. We reported that the rate of bleaching of [tetraphenylporphyrinato]iron under the coupled oxidation conditions followed the Hammett equation with a positive reaction constant $\rho = 0.30$ [9]. These Hammett studies showed that a nucleophilic step is included for the formation of bilindione. We previously proposed that the 19-benzoylbilatrienone iron complex was formed as an intermediate (Scheme 2). O_2 was activated on the iron and nucleophilic attack of $Fe–O–O^-$ occurs to the acyl group in the 19 position in a similar fashion to Baeyer–Villiger oxidation to result in bilindione [11]. In the typical Baeyer–Villiger oxidation of acetophenones, the Hammett reaction constant was reported to be negative, indicating that electron-donating groups accelerated the reaction [14]. The positive sign of the reaction constant of the coupled oxidation could imply that the rate-limiting step is nucleophilic attack of iron-bound oxygen to the carbonyl group.

Coupled oxidation of A3B type porphyrin

We investigated the coupled oxidation of iron tetraphenylporphyrin bearing a nitro group in one of the phenyl groups, an A3B type porphyrin. 5-(4-Nitrophenyl)-10,15,20-triphenylporphyrin was synthesized from tetraphenylporphyrin and white fuming nitric acid [15]. Coupled oxidation of the iron complex **4** was carried out and biladien-*ab*-1-one **5** and bilindione **6** were separated on silica gel column chromatography (Scheme 3).

The total yields of biladien-*ab*-1-one **5a–5d** and bilindione **6a–6c** were 15.7% and 0.5%, respectively. ^{1}H NMR studies showed that biladien-*ab*-1-one **5a–5d** were formed statistically, while bilindione **6c** was formed selectively in the reaction. In the ^{1}H NMR of a mixture **5a–5d**, the resonances of the phenyl protons appeared at 7.58, 7.71, 7.75, 7.88, 8.01, 8.23 and 8.30 (overlapped three signals) ppm. One of the characteristic resonances of phenyl protons is the benzoyl *ortho* protons giving the downfield resonance. The resonance of benzoyl *ortho* proton in 19-benzoyl-5,10,15-triphenylbiladien-*ab*-1-one was observed at 7.81 ppm [8]. We thus assigned the resonance at 7.88 ppm to the benzoyl *ortho* protons of **5a–5c**. This resonance had no COSY correlation with any further downfield resonances, supporting the assignment. The COSY experiments displayed that the following pairs of resonances are assigned to vicinal protons: resonances at 7.58 ppm and 8.23 ppm, those at 7.71 ppm and 8.30 ppm, those at 7.75 ppm and 8.30 ppm, and those at 8.01 ppm and



Scheme 1. Coupled oxidation of [tetraarylporphyrinato]iron **1a–h**

Table 1. Isolated yields (%) of biladien-*ab*-1-ones and bilindiones of coupled oxidation of tetraarylporphyrins bearing various substituents

Substituent	Biladien-*ab*-1-one **2**	Bilindione **3**
p-OCH_3 (**a**)	85[a]	1.9[b]
p-CH_3 (**b**)	37	1.7
H (**c**)	59[b]	4.1[b]
p-F (**d**)	72	3.5
p-Cl (**e**)	35	2.8
p-$COOCH_3$ (**f**)	44[a]	5.9[b]
p-CF_3 (**g**)	32	4.1
p-CN (**h**)	28[a]	6.7[b]

[a] Taken from reference 9. [b] Taken from Ref. 10.

8.30 ppm. The furthest downfield resonances at 8.01 ppm and 8.30 ppm were assigned to *ortho* and *meta* phenyl protons of **5d**, respectively, because of the two electron-withdrawing groups in a benzene ring. The rest of the resonances at 7.58, 7.71 and 7.75 ppm and at 8.23, 8.30 and 8.30 ppm were assigned to *ortho* and *meta* phenyl protons, respectively, in 4-nitrobenzoyl group of other structural isomers **5a–5c**. On the basis of the integrals of the benzoyl protons, the ratio of the yield of **5d** to that of **5a–5c** was *ca*. one to two. Although there is a slight preference for the cleavage at the *meso*-position with a 4-nitrophenyl group, we can conclude that the oxidation resulting in biladienone occurs rather statistically in any of the *meso*-positions of **4**. To determine which *meso* phenyl group was cleaved to give bilindione **6**, a TOF-MS spectrum of a mixture of bilindione **6a–6c** was recorded.

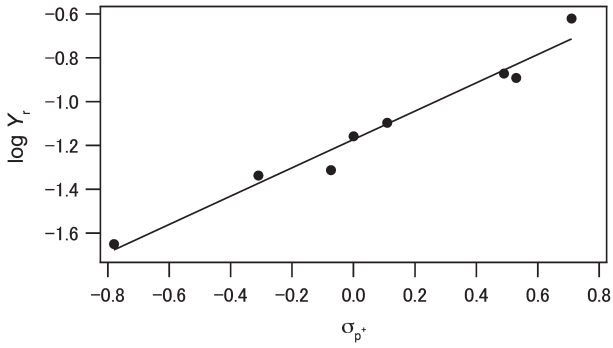
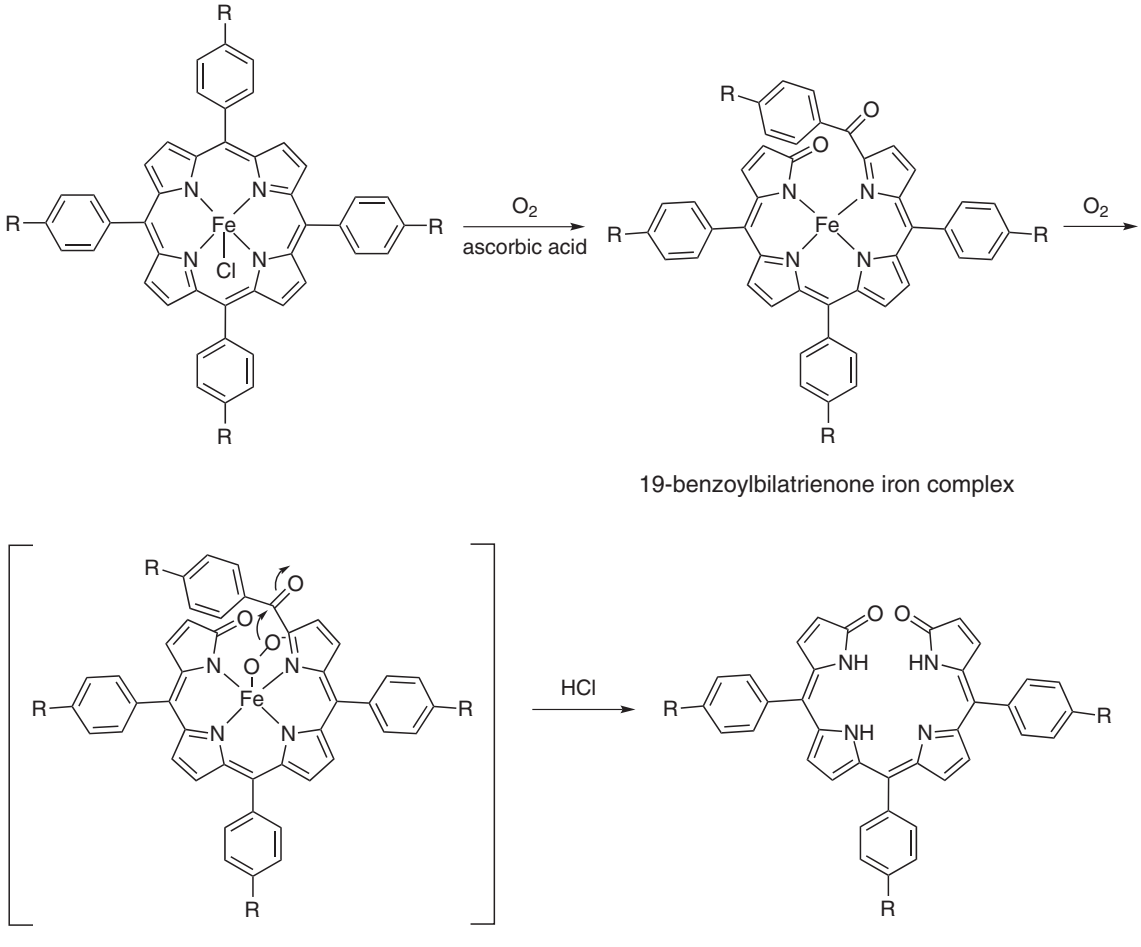


Fig. 1. Hammett plots of the ratios of isolated yields of **3** to those of **2** by coupled oxidation of **1** against Hammett substituent constants σ_p^+. The reaction constant $\Delta\rho$ was 0.64 ± 0.04. σ_p^+ (CN) = 0.71, σ_p^+ (CF_3) = 0.53, σ_p^+ (COOMe) = 0.49, σ_p^+ (Cl) = 0.11, σ_p^+ (H) = 0, σ_p^+ (F) = -0.073, σ_p^+ (Me) = -0.31, σ_p^+ (OMe) = -0.78

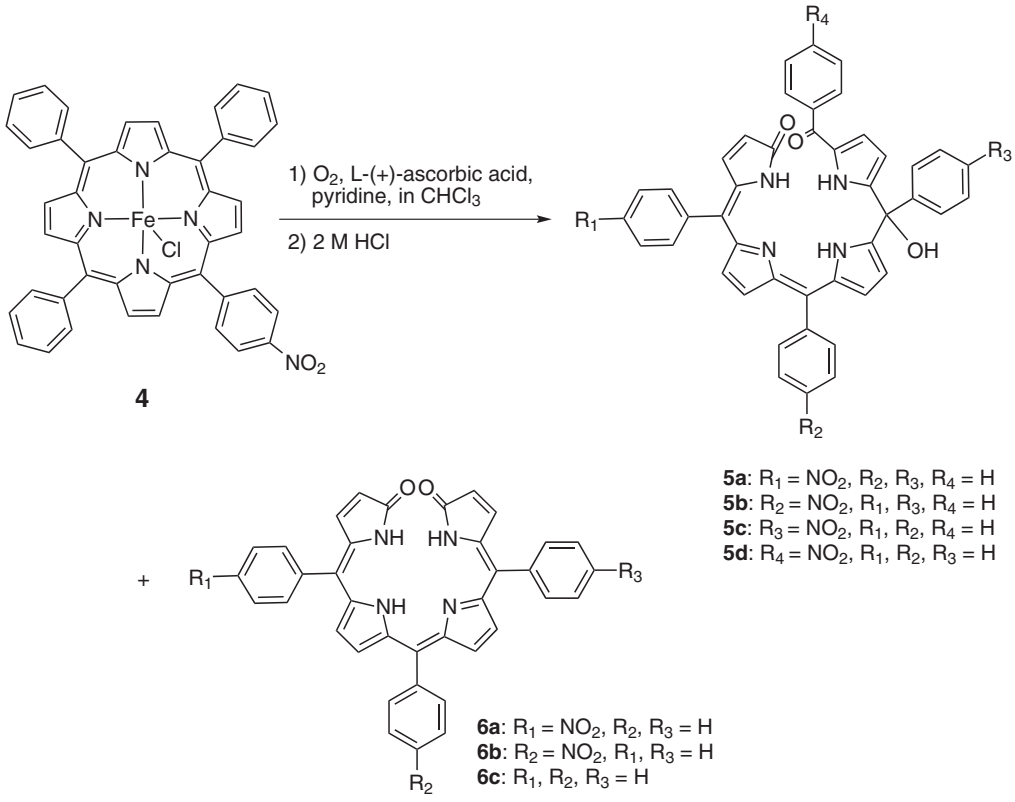
It showed signals at *m/z* 559 (relative intensity 100) and at *m/z* 604 (5). The former signal is attributable to **6c** (MH^+), while the latter one to **6a** and **6b** (MH^+), showing that **6c** is the major product. Therefore, the nitrophenyl group was preferentially cleaved.

We previously reported that regioselectivity in coupled oxidation of porphyrin **7** bearing a CF_3 group in the β-pyrrole position occurred preferentially at the electronically negative *meso*-position [6]. To determine the electron density of the *meso* carbons of **4**, molecular orbital calculations were performed at the B3LYP/6-31G(D) level. Atomic charges according to Mulliken population analysis [16] of the *meso*-position are listed in Table 2. The atomic charge at C5 position substituted with 4-nitrophenyl group was higher than the other *meso*-positions. The porphyrin plane and phenyl plane are not planar, and the direct conjugation of the nitro group with π electron systems of the porphyrin ring was hindered. The higher electron density at C5 can be attributed to the through-space induced dipole moment in the porphyrin π-electrons by the nitro group. However, electronic polarization seems much smaller than that of β-CF_3 porphyrin **7**, in which the *meso* Mulliken electron density ranged from -0.28 to -0.38. Therefore, MO calculations predict that there are smaller electronic effects on selectivity of cleavage of **4**.

The low yield of bilindione (0.5%) is consistent with a two-step mechanism of bilindione, where the



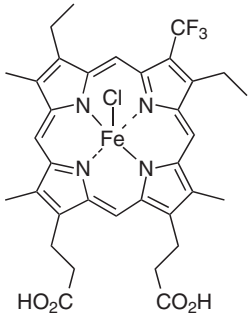
Scheme 2. Two-step mechanism of bilindione formation



Scheme 3. Coupled oxidation of mono-nitro substituted iron tetraphenylporphyrin

Table 2. Atomic charges for [5-(4-nitrophenyl)-10,15,20-triphenylporphyrinato]iron(II) in the singlet state

Position	Mulliken population analysis
C5 (4-nitrophenyl)	-0.0598
C10 (phenyl)	-0.0563
C15 (phenyl)	-0.0 562
C20 (phenyl)	-0.0566



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statistical attack of the *meso*-positions is followed by the nucleophilic cleavage of the phenyl group, where opposite electronic effects are operating.

EXPERIMENTAL

Commercially available reagents were used as received. Chromatographic separation of 19-substituted bilinones was performed using silica gel 60N, spherical neutral with particle size 40–50 μm, Kanto Chemical Company. The free base porphyrins were prepared by refluxing a propionic acid solution of pyrrole and *para*-substituted benzaldehyde for 30 min. Mono-nitro substituted tetraphenylporphyrin was synthesized from tetraphenylporphyrin and white fuming nitric acid [15]. Iron porphyrins were prepared by refluxing a DMF solution of porphyrin and iron(II) chloride for 4 h. 1D NMR and 2D NMR experiments were performed with a JEOL JNM-ECA500 spectrometer. Tetramethylsilane was used as an internal standard of ^{1}H and ^{13}C NMR spectra. ^{1}H NMR and ^{13}C NMR signals were assigned using ^{1}H-^{1}H COSY, ROESY, HMBC and HMQC spectra. UV-visible spectra were recorded on a SHIMADZU MultiSpec-1500 spectrophotometer and an Agilent 8453 UV-visible spectrophotometer. Matrix-assisted laser desorption-ionization time-of-flight mass (MALDI-TOF MS) spectra were recorded on a Bruker Daltonics Autoflex Speed spectrometer. Fast atom bombardment mass (FAB MS) spectra were recorded on a JEOL JMS-700 spectrometer. Preparation and spectroscopic data of biladien-*ab*-1-ones **2a**, **2c**, **2f**, **2h** and bilindiones **3a**, **3c**, **3f**, **3h** were reported elsewhere [8–10].

(4Z,9Z)-1,15,21,24-tetrahydro-19-(4-methylbenzoyl)-15-hydroxy-5,10,15-tris(4-methylphenyl)-23*H*-bilin-1-one (2b) and (4Z,9Z,15Z)-5,10,15-tris(4-methylphenyl)-(21*H*,23*H*,24*H*)-1,19,21,24-tetrahydro-1,19-bilindione (3b). Chloroform (100 mL) was placed in a 500-mL three-necked flask, and O_2 was bubbled for 30 min. [5,10,15,20-Tetrakis(4-methylphenyl)porphyrinato]iron(III) chloride (500 mg, 0.657 mmol), ascorbic acid (2.3 g, 13 mmol), and pyridine (28 mL, 0.34 mol) were added, and the mixture was stirred at room temperature for 1 h with O_2 bubbling. The reaction was quenched by adding 2 M HCl (270 mL), and the solution was stirred for 1 h at room temperature. The chloroform solution was separated, washed with water twice, and the organic layer was dried over Na_2SO_4. After the Na_2SO_4 was filtered off, the organic layer was evaporated to give a mixture of biladien-*ab*-1-one, bilindione and other pigments. Silica gel column chromatography eluted with chloroform:acetone (9:1) afforded 178 mg (37.4%) of **2b** as a less polar fraction. Silica gel column chromatography using chloroform:acetone (9:1) yielded 6.8 mg (1.7%) of bilindione **3b** as a more polar fraction. **2b.** ^{1}H NMR (500 MHz, chloroform-*d*): δ_H, ppm 2.32 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 6.13 (d, J = 5.75 Hz, 1H, pyrrole), 6.15–6.18 (m, 2H, pyrrole), 6.33 (d, J = 4.60 Hz, 1H, pyrrole), 6.37 (s, 1H, OH), 6.48 (d, J = 4.00 Hz, 1H, pyrrole), 6.78–6.80 (m, 2H, pyrrole), 6.87 (d, J = 5.20 Hz, 1H, pyrrole), 7.15 (d, J = 8.00 Hz, 2H, phenylene), 7.20–7.24 (m, 8H, phenylene), 7.37 (d, J = 8.00 Hz, 2H, phenylene), 7.40 (d, J = 8.00 Hz, 2H, phenylene), 7.77 (d, J = 8.00 Hz, 2H, phenylene), 10.16 (bs, 1H, NH), 10.87 (bs, 1H, NH), 12.43 (bs, 1H, NH). ^{13}C NMR (125 MHz, chloroform-*d*): δ_C, ppm 21.2, 21.3, 21.5, 21.6, 74.9, 109.8, 111.8, 119.5, 121.5, 124.2, 125.4, 125.9, 127.0, 128.6, 128.9, 129.0, 129.2, 129.3, 130.5, 131.0, 131.7, 133.4, 134.4, 134.5, 135.8, 137.8, 138.2, 138.5, 139.2, 139.9, 140.8, 142.2, 142.6, 143.1, 149.6, 150.2, 164.5, 173.3, 184.4. HRMS (FAB): *m/z* 720.3083 (calcd. for $C_{48}H_{40}O_3N_4$ 720.3100). UV-vis ($CHCl_3$, 25 °C): λ_{max}, nm (ε_{max}, $M^{-1}.cm^{-1}$) 321 (3.03×10^4), 360 (3.26×10^4), 568 (2.08×10^4). **3b.** ^{1}H NMR (500 MHz, chloroform-*d*): δ_H, ppm 2.32 (s, 6H, CH_3), 2.45 (s, 3H, CH_3), 6.22 (d, J = 5.70 Hz, 2H, pyrrole H-2), 6.48 (d, J = 4.60 Hz, 2H, pyrrole H-7), 6.74 (d, J = 4.60 Hz, 2H, pyrrole H-8), 7.00 (d, J = 5.70 Hz, 2H, pyrrole H-3), 7.16 (d, J = 8.00 Hz, 4H, 5,15-phenylene H-3), 7.25 (overlapped $CHCl_3$, 4H, 5,15-phenylene H-2′), 7.29 (d, J = 7.40 Hz, 2H, 10-phenylene H-3′), 7.41 (d, J = 8.00 Hz, 2H, 10-phenylene H-2′), 8.23 (bs, 2H, NH), 12.05 (bs, 1H, NH). ^{13}C NMR (125 MHz, chloroform-*d*): δ_C, ppm 21.3, 21.4, 119.1, 121.3, 123.8, 128.7, 129.0, 130.0, 131.5, 132.9, 133.9, 137.8, 138.1, 138.4, 139.9, 143.2, 153.4, 171.6. MS (MALDI TOF): *m/z* 601 (calcd. for $[M + H]^+$ 601). HRMS (FAB): *m/z* 600.2532 (calcd. for $C_{40}H_{32}O_2N_4$ 600.2525). UV-vis ($CHCl_3$, 25 °C): λ_{max}, nm (ε_{max}, $M^{-1}.cm^{-1}$) 351 (1.9×10^4), 408 (3.7×10^4), 623 (1.6×10^4).

(4Z,9Z)-1,15,21,24-tetrahydro-19-(4-fluorobenzoyl)-15-hydroxy-5,10,15-tris(4-fluorophenyl)-23*H*-bilin-1-one (2d) and (4Z,9Z,15Z)-5,10,15-tris(4-fluorophenyl)-(21*H*,23*H*,24*H*)-1,19,21,24-tetrahydro-1,19-bilindione (3d). Coupled oxidation was performed using [5,10,15,20-tetrakis(4-fluorophenyl)porphyrinato] iron(III) chloride (500 mg, 0.631 mmol), ascorbic acid (2.3 g, 13 mmol), and pyridine (27 mL, 0.33 mol), according to the procedures reported above. Biladien-*ab*-1-one **2d** was isolated by silica gel column chromatography eluted with chloroform:acetone (95:5), yielding 346 mg (71.9%) of biladien-*ab*-1-one **2d**. Further purification by silica gel column chromatography using chloroform:ethyl acetate (1:1) yielded 14 mg (3.5%) of bilindione **3d**. **2d.** ^{1}H NMR (500 MHz, chloroform-*d*): δ_H, ppm 6.15–6.17 (m, 2H, pyrrole), 6.21 (d, J = 5.70 Hz, 1H, pyrrole), 6.31 (d, J = 4.60 Hz, 1H, pyrrole), 6.39 (s, 1H, OH), 6.47 (d, J = 4.00 Hz, 1H, pyrrole), 6.78 (d, J = 4.60 Hz, 1H, pyrrole), 6.81 (d, J = 4.00 Hz, 2.3 Hz, 1H, pyrrole), 6.87 (d, J = 5.70 Hz, 1H, pyrrole), 7.06 (t, J = 8.60 Hz, 2H, phenylene), 7.13–7.18 (m, 6H, phenylene), 7.34 (dd, J = 8.60 Hz, 5.15 Hz, 2H, phenylene), 7.47 (dd, J = 9.20 Hz, 5.15 Hz, 2H, phenylene), 7.51 (dd, J = 8.60 Hz, 5.15 Hz, 2H, phenylene), 7.91 (dd, J = 8.60 Hz, 5.15 Hz, 2H, phenylene), 9.98 (bs, 1H, NH), 10.88 (bs, 1H, NH), 12.38 (bs, 1H, NH). ^{13}C NMR (125 MHz, chloroform-*d*): δ_C, ppm 74.5, 110.3, 111.95, 115.0, 115.2, 115.4, 119.6, 120.0, 124.7, 125.0, 126.1, 129.0, 129.1, 130.7, 131.47, 131.54, 132.0, 132.3, 137.7, 132.8, 133.2, 133.26, 133.32, 134.5, 134.7, 139.5, 139.7, 141.6, 142.8, 149.8, 149.9, 161.7, 161.8, 162.7, 163.6, 163.7, 164.0, 164.7, 164.9, 166.0, 173.2, 183.1. HRMS (FAB): *m/z* 736.2093 (calcd. for $C_{44}H_{28}O_3N_4F_4$ 736.2098). UV-vis ($CHCl_3$, 25 °C): λ_{max}, nm (ε_{max}, $M^{-1}.cm^{-1}$) 350 (3.23×10^4), 566 (2.08×10^4). **3d.** ^{1}H NMR (500 MHz, chloroform-*d*): δ_H, ppm 6.26 (d, J = 5.75 Hz, 2H, pyrrole H-2), 6.49 (d, J = 4.60 Hz, 2H, pyrrole H-7), 6.73 (d, J = 4.60 Hz, 2H, pyrrole H-8), 6.99 (d, J = 5.75 Hz, 2H, pyrrole H-3), 7.08 (t, J = 8.60 Hz, 4H, 5,15-phenylene H-2′), 7.20 (t, J = 8.60 Hz, 2H, 10-phenylene H-2′), 7.36 (dd, J = 5.75 Hz, 2.85 Hz, 4H, 5,15-phenylene H-3′), 7.51 (dd, J = 5.75 Hz, 2.85 Hz, 2H, 10-phenylene H-3′), 8.19 (bs, 2H, NH), 12.02 (bs, 1H, NH). ^{13}C NMR (125 MHz, chloroform-*d*): δ_C, ppm 115.23, 115.35, 115.40, 115.53, 117.6, 121.7, 124.3, 130.1, 131.8, 132.6, 133.18, 133.24, 133.31, 137.7, 138.3, 138.7, 139.6, 143.3, 153.4, 162.0, 162.7, 163.9, 164.7, 171.4. MS (MALDI TOF): *m/z* 613 (calcd. for $[M + H]^+$ 613). HRMS (FAB): *m/z* 613.1832 (calcd. for $C_{37}H_{24}O_2N_4F_3$ 613.1851). UV-vis ($CHCl_3$, 25 °C): λ_{max}, nm (ε_{max}, $M^{-1}.cm^{-1}$) 338 (1.26×10^4), 402 (2.52×10^4), 623 (1.12×10^4).

(4Z,9Z)-1,15,21,24-tetrahydro-19-(4-chlorobenzoyl)-15-hydroxy-5,10,15-tris(4-chlorophenyl)-23*H*-bilin-1-one (2e) and (4Z,9Z,15Z)-5,10,15-tris(4-chlorophenyl)-(21*H*,23*H*,24*H*)-1,19,21,24-tetrahydro-1,19-bilindione (3e). Coupled oxidation was performed using [5,10,15,20-tetrakis(4-chlorophenyl)

porphyrinato]iron(III) chloride (500 mg, 0.594 mmol), ascorbic acid (2.1 g, 12 mmol), and pyridine (25 mL, 0.33 mol). Biladien-*ab*-1-one **2e** was isolated by silica gel column chromatography eluted with chloroform:acetone (95:5), yielding 165 mg (34.9%) of biladien-*ab*-1-one **2e**. Further purification by silica gel column chromatography using chloroform:ethyl acetate (1:1) yielded 11 mg (2.8%) of bilindione **3e**. **2e.** ^{1}H NMR (500 MHz, chloroform-*d*): δ_H, ppm 6.06 (dd, J = 4.00 Hz, 2.50 Hz, 1H, pyrrole), 6.10 (d, J = 5.75 Hz, 1H, pyrrole), 6.13 (d, J = 4.00 Hz, 1H, pyrrole), 6.27 (d, J = 4.60 Hz, 1H, pyrrole), 6.41 (d, J = 4.00 Hz, 1H, pyrrole), 6.43 (s, 1H, OH), 6.70 (dd, J = 4.00 Hz, 2.50 Hz, 1H, pyrrole), 6.74 (d, J = 4.60 Hz, 1H, pyrrole), 6.78 (d, J = 5.75 Hz, 1H, pyrrole), 7.23 (d, J = 8.60 Hz, 2H, phenylene), 7.27 (d, J = 8.60 Hz, 2H, phenylene), 7.37–7.45 (m, 10H, phenylene), 7.72 (d, J = 8.60 Hz, 2H, phenylene), 10.65 (bs, 1H, NH), 10.73 (bs, 1H, NH), 12.40 (bs, 1H, NH). ^{13}C NMR (125 MHz, chloroform-*d*): δ_C, ppm 74.4, 110.4, 112.0, 119.65, 119.81, 124.85, 124.99, 126.3, 128.28, 128.56, 128.63, 130.5, 130.7, 131.8, 132.4, 132.7, 134.51, 134.59, 134.72, 134.76, 135.6, 136.0, 136.6, 137.2, 138.1, 139.7, 141.3, 142.1, 142.7, 149.5, 149.8, 164.9, 173.1, 183.3. HRMS (FAB): *m/z* 800.0889 (calcd. for $C_{44}H_{28}O_3N_4{}^{35}Cl_4$ 800.0916). UV-vis ($CHCl_3$, 25 °C): λ_{max}, nm (ε_{max}, $M^{-1}.cm^{-1}$) 350 (3.55×10^4), 567 (2.20×10^4). **3e**. ^{1}H NMR (500 MHz, chloroform-*d*): δ_H, ppm 6.27 (d, J = 5.75 Hz, 2H, pyrrole H-2), 6.50 (d, J = 4.60 Hz, 2H, pyrrole H-7), 6.73 (d, J = 4.60 Hz, 2H, pyrrole H-8), 7.00 (d, J = 5.75 Hz, 2H, pyrrole H-3), 7.35 (d, J = 8.30 Hz, 4H, 5,15-phenylene), 7.48 (d, J = 8.30 Hz, 4H, 5,15-phenylene), 7.48 (m, 4H, 10-phenylene), 8.28 (bs, 2H, NH), 12.05 (bs, 1H, NH). ^{13}C NMR (125 MHz, chloroform-*d*): δ_C, ppm 117.4, 121.7, 124.6, 128.6, 128.8, 130.2, 132.7, 132.9, 134.3, 135.0, 137.8, 138.8, 143.2, 153.2, 171.5. MS (MALDI TOF): *m/z* 661 (calcd. for $[M + H]^+$ 661). HRMS (FAB): 660.0863 (calcd. for $C_{37}H_{23}O_2N_4{}^{35}Cl_3$ *m/z* 660.0887). UV-vis ($CHCl_3$, 25 °C): λ_{max}, nm (ε_{max}, $M^{-1}.cm^{-1}$) 344 (2.05×10^4), 404 (4.17×10^4), 627 (1.87×10^4).

(4Z,9Z)-1,15,21,24-tetrahydro-19-(4-trifluoromethylbenzoyl)-15-hydroxy-5,10,15-tris(4-trifluoromethylphenyl)-23*H*-bilin-1-one (2g) and (4Z, 9Z, 15Z)-5,10,15-tris(4-trifluoromethylphenyl)-(21*H*,23*H*,24*H*)-1,19,21,24-tetrahydro-1,19-bilindione (3g). Coupled oxidation was performed using [5,10,15,20-tetrakis(4-trifluoromethylphenyl)porphyrinato]iron(III) chloride (500 mg, 0.512 mmol), ascorbic acid (2.1 g, 12 mmol), and pyridine (21 mL, 0.27 mol). Biladien-*ab*-1-one **2g** was isolated by silica gel column chromatography eluted with chloroform:acetone (95:5), yielding 153 mg (32.0%) of biladien-*ab*-1-one **2g**. Further purification by silica gel column chromatography using chloroform:ethyl acetate (1:1) yielded 16 mg (4.1%) of bilindione **3g**. **2g.** ^{1}H NMR (500 MHz, chloroform-*d*): δ_H, ppm 6.08 (dd, J = 4.00 Hz, 2.85 Hz, 1H, pyrrole), 6.13 (d, J = 5.75 Hz, 1H, pyrrole), 6.15 (d, J = 4.00 Hz, 1H, pyrrole), 6.25 (d, J = 4.60 Hz, 1H, pyrrole), 6.40 (d, J = 4.00Hz, 1H, pyrrole), 6.54 (s, 1H, OH), 6.71 (dd, J = 4.00 Hz, 2.85 Hz, 1H, pyrrole), 6.73 (d, J = 4.60 Hz, 1H, pyrrole), 6.78 (d, J = 5.75 Hz, 1H, pyrrole), 7.45 (d, J = 8.00 Hz, 2H, phenylene), 7.62 (d, J = 8.60 Hz, 4H, phenylene), 7.67–7.75 (m, 8H, phenylene), 7.85 (d, J = 8.00 Hz, 2H, phenylene), 10.71 (bs, 1H, NH), 10.77 (bs, 1H, NH), 12.53 (bs, 1H, NH). ^{13}C NMR (125 MHz, chloroform-*d*): δ_C, ppm 74.6, 110.9, 112.1, 119.7, 122.9, 124.96, 125.03, 125.33, 125.40, 126.0, 126.7, 127.5, 129.4, 130.6, 130.9, 131.0, 130.9, 131.0, 131.52, 131.60, 131.8, 135.1, 137.4, 140.0, 140.3, 140.6, 140.8, 141.3, 142.7, 147.2, 148.9, 150.1, 165.3, 173.2, 183.5. HRMS (FAB): *m/z* 936.1963 (calcd. for $C_{48}H_{28}O_3N_4F_{12}$ 936.1970). UV-vis ($CHCl_3$, 25 °C): λ_{max}, nm (ε_{max}, $M^{-1}.cm^{-1}$) 344 (3.94×10^4), 565 (2.36×10^4). **3g.** ^{1}H NMR (500 MHz, chloroform-*d*): δ_H, ppm 6.22 (d, J = 5.70 Hz, 2H, pyrrole H-2), 6.50 (d, J = 4.60 Hz, 2H, pyrrole H-7), 6.71 (d, J = 4.60 Hz, 2H, pyrrole H-8), 6.96 (d, J = 5.75 Hz, 2H, pyrrole H-3), 7.51 (d, J = 8.00 Hz, 4H, 5,15-phenylene H-2′), 7.65 (d, J = 8.00 Hz, 6H, 5,10,15-phenylene H-3′), 7.77 (d, J = 8.00 Hz, 2H, 10-phenylene H-2′), 8.47 (bs, 2H, NH), 11.94 (bs, 1H, NH). ^{13}C NMR (125 MHz, chloroform-*d*): δ_C, ppm 117.0, 121.9, 122.8, 124.8, 124.9, 125.1, 125.3, 130.1, 130.6, 130.8, 131.6, 131.9, 137.6, 139.1, 139.3, 140.1, 143.1, 153.3, 171.5. MS (MALDI TOF): *m/z* 763 (calcd. for $[M + H]^+$ 763). HRMS (FAB): *m/z* 763.1764 (calcd. for $C_{40}H_{24}O_2N_4F_9$ 763.1755). UV-vis ($CHCl_3$, 25 °C): λ_{max}, nm (ε_{max}, $M^{-1}.cm^{-1}$) 397 (3.36×10^4), 626 (1.53×10^4).

Coupled oxidation of [5-(4-nitrophenyl)-10,15,20-triphenylporphyrinato]iron(III) chloride. Chloroform (100 mL) was placed in a 500-mL three-necked flask, and O_2 was bubbled for 30 min. [5-(4-Nitrophenyl)-10,15,20-triphenylporphynato]iron(III) chloride (500 mg, 0.667 mmol), ascorbic acid (2.4 g, 14 mmol), and pyridine (28 mL, 0.35 mol) were added, and the mixture was stirred at room temperature for 1 h with O_2 bubbling. The reaction was quenched by adding 2 M HCl (270 mL), and the solution was stirred for 1 h at room temperature. The chloroform solution was separated, washed with water twice, and the organic layer was dried over Na_2SO_4. After the Na_2SO_4 was filtered off, the organic layer was evaporated to give a mixture of biladien-*ab*-1-one, bilindione and other pigments. Biladien-*ab*-1-one and bilindione were isolated by silica gel column chromatography eluted with chloroform:acetone (95:5). Further purification by silica gel column chromatography using chloroform:acetone (98:2) yielded 74.6 mg (15.7%) of biladien-*ab*-1-one **5a–5d**. Further purification by silica gel column chromatography using dichloromethane: acetone (85:15) yielded 1.7 mg (0.5%) of bilindione **6a–6c**.

CONCLUSION

Iron complexes of tetraarylporphyrins having various substituents in the *para*-position was oxidized with

dioxygen in the presence of ascorbic acid and pyridine to afford biladien-*ab*-1-one and bilindione. The Hammett plot of the ratios of yields of the latter to the former products yielded a straight line with a positive slope. A nucleophilic step is included in the formation of bilindione. Oxidation of the tetraphenylporphyrin iron complex with one nitro group showed that biladien-*ab*-1-one formed with the statistical attack at the *meso*-positions, while bilindione was formed with the preferential attack at the *meso*-position bearing a 4-nitrophenyl group.

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Supporting information

Preparation of **2b**, **2d**, **2e**, **2g**, **3b**, **3d**, **3e**, and **3g**, ^{1}H and ^{13}C NMR spectra of **2b**, **2d**, **2e**, **2g**, **3b**, **3d**, **3e**, **3g**, **5a–5d**, and **6a–6c** (Scheme S1, Figs S1–S20) is given in the supplementary material. This material is available free of charge *via* the Internet at http://www.worldscinet.com/jpp/jpp.shtml.

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