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Synthesis of oxo-, thioxo- and methylene-substituted bacteriochlorins by modifying chlorophyll-*a* and their electronic absorption in visible and near-infrared regions

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ABSTRACT

Regioisomerically pure 7/8,13^1-dioxo-bacteriochlorins prepared by modification of naturally occurring chlorophyll-*a* were reacted with Lawesson's reagent in toluene at room temperature or reflux to give 7/8-oxo-13^1-thioxo- or 7/8,13^1-dithioxo-products, respectively. The 13^1-thioxo moiety of the latter products was selectively transformed to the oxo group to afford 7/8-thioxo-13^1-oxo-bacteriochlorins. The remaining 7/8-thioxo moiety was treated with diazomethane to be successfully converted to the methylene group. Electronic absorption and circular dichroism spectra of all the synthetic bacteriochlorins were measured in 20% (v/v) tetrahydrofuran and hexane. Comparison of these spectra showed that thiocarbonylation induced red-shifts of all the absorption maxima in visible and near-infrared regions and 7-oxo-derived bacteriochlorins afforded their maxima at a longer wavelength than those of the corresponding 8-substituted regioisomers.

1. Introduction

Regulation of electronic absorption spectra in photosynthetic apparatus is important for phototrophs to live in various environments. Chlorophylls (Chls) and bacteriochlorophylls (BChls) are major pigments in the photosynthetic antennas and reaction centers [1]. Light-harvesting and energy-transferring (or exciton migration) processes occur in the former and electron-transferring (or charge separation) successively proceeds in the latter. Several factors control the efficiency in absorbing light and transferring the photoexcited (singlet) energy [2]. The change of molecular structures of the above (B)Chl pigments is the most effective. The π-conjugation degree in the chlorophyllous skeletons greatly affects their spectra. Typically, the absorption band situated at the longest wavelength, called a Qy band is bathochromically shifted with a decrease of the conjugation degree: Qy maxima (nm unit) of Chls possessing a fully π-conjugated porphyrin < those of chlorins with a C17—C18 single bond < those of bacteriochlorins with two single bonds at C7—C8 and C17—C18 (see the left drawing of Fig. 1) [3]. Usual oxygenic phototrophs have Chls possessing a chlorin π-system and use primarily visible (VIS) light, while anoxygenic ones have BChls with a bacteriochlorin chromophore as a major pigment and can utilize near-infrared (NIR) light. Substituents on the two upper pyrrole rings of chlorophyllous macrocycles, called A- and B-rings, also regulated the electronic absorption properties [3]. In naturally occurring (B)Chls, vinyl, formyl, acetyl, methoxycarbonyl and ethylidene groups are found as the π-conjugatable substituents at the 2-, 3-, 7-, and 8-positions [1,4].

Due to the variety of electronic absorption in natural (B)Chls, semi-synthetic (B)Chl derivatives are applied to artificial photoresponsive systems including photonic imaging and therapeutic agents [5–7], optical sensors [8,9], and solar cells [10,11]. Bacteriochlorins are effective for development of NIR-light driving systems. Since bacteriochlorin π-skeletons in natural BChls are easily altered to chlorin π-systems, more chemically stable bacteriochlorins have been produced [12–16]. Oxo-bacteriochlorins (e.g., **1** and **6**, see center and right of Fig. 1) are one class of such stable pigments to give Qy maxima at around 700 nm in a solution [8,10,14,17,18].

Some carbonyl groups are converted to the corresponding thiocarbonyl groups by treatment of Lawesson's reagent [19]. The transformation affects electronic absorption spectra of the pigments π-conjugated with the (thio)carbonyl moiety. Substitution of the carbonyl oxygen atom in oxo-(bacterio)chlorins with a sulfur atom shifted their Qy maxima to a longer wavelength [17,20,21]. Here we report synthesis of (di)thioxo-bacteriochlorins **2**–**4**/**7**–**9** by modifying Chl-*a* and their absorption and circular dichroism (CD) spectra in the VIS–NIR region. Additionally, preparation of bacteriochlorins **5**/**10** possessing an exo-methylene moiety on the B-ring

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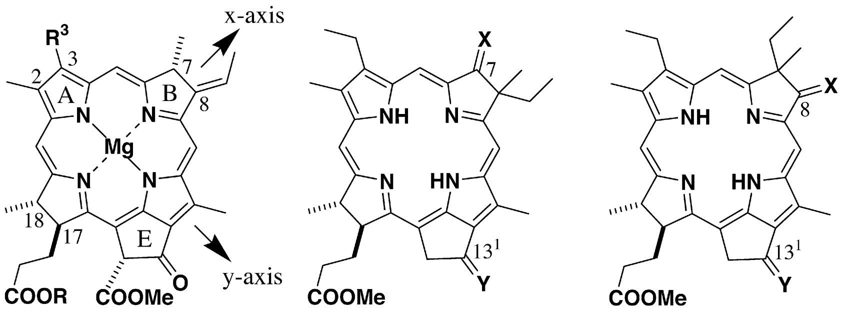

BChl-*b*: R^3 = $COCH_3$, R = phytyl
BChl-*g*: R^3 = CH=CH_2, R = farnesyl

1: X = Y = O
2: X = O, Y = S
3: X = Y = S
4: X = S, Y = O
5: X = CH_2, Y = O

6: X = Y = O
7: X = O, Y = S
8: X = Y = S
9: X = S, Y = O
10: X = CH_2, Y = O

Fig. 1. Molecular structures of naturally occurring BChls-*b*/*g* (left) as well as synthetic 7/8,13^1-dioxo-bacteriochlorin derivatives **1**–**5**/**6**–**10** (middle/right).

by treatment of **4**/**9** with diazomethane is described. Substitution effect of **1**–**10** on their VIS–NIR absorption spectra is also discussed.

2. Experimental

2.1. General

Electronic absorption and CD spectra in ultraviolet (UV), VIS and NIR regions were measured in air-saturated solvents at room temperature on a Hitachi U-3500 spectrophotometer and a Jasco J-720W spectropolarimeter, respectively. Fluorescence emission data were collected using Hamamatsu Photonics absolute PL and lifetime measurement systems C9920-03G and C7990S. ^1H NMR spectra were recorded on a JEOL AL-400 (400 MHz) or ECA-600 (600 MHz) spectrometer; as an internal reference, a residual proton signal (δ = 7.26 ppm) in $CDCl_3$ was used. Time-of-flight (TOF) mass data were obtained using direct laser desorption/ionization by a Shimadzu AXIMA-CFR plus spectrometer. HRMS data were recorded by a JEOL GCmate II spectrometer with fast atomic bombardment (FAB) ionization; FAB-MS samples were dissolved in CH_2Cl_2, *m*-nitrobenzyl alcohol was used as the matrix and PEG600 was added as an external reference. Flash column chromatography (FCC) was performed with silica gel (Merck, Kieselgel 60). High performance liquid chromatography (HPLC) was done with a Shimadzu LC-10ADvp pump and SPD-M10Avp photodiode-array detector.

Methyl 7-demethyl-8-methyl-7-oxo-mesopyropheophorbide-*a* (**1**) and methyl 8-deethyl-7-ethyl-8-oxo-mesopyropheophorbide-*a* (**6**) were prepared according to reported procedures [18]. All the reactions were done in the dark under nitrogen. The purity of all the compounds **1**–**10** was checked by HPLC (see Figure S1 in supplementary data). Just after purification by HPLC (Cosmosil $5C_{18}$-AR-II, 4.6 mm $\Phi \times 150$ mm, 20% THF/hexane, 2.5 mL/min), electronic absorption and CD spectra of **1**–**10** were measured in the eluted solvent.

2.2. Synthesis of 7,13^1-dioxo-bacteriochlorin derivatives **2**–**5**

2.2.1. Methyl 7-demethyl-13^1-deoxo-8-methyl-7-oxo-13^1-thioxo-mesopyropheophorbide-*a* (**2**)

To a solution of **1** (8*R*:*S* = 1:1, 50 mg, 88 μmol) in toluene (12 mL) was added Lawesson's reagent (50 mg, 124 μmol), then the solution was stirred at room temperature overnight. The reaction mixture was concentrated in vacuo. The resulting residue was purified by FCC (CH_2Cl_2) to give **2** in 79% yield as a 1:1 8-epimeric mixture: brown solid; UV–VIS–NIR (CH_2Cl_2) λ_{max} 752 (relative intensity, 100), 689 (25), 631 (10), 568 (15), 532 (13), 444 (67), 422 (64), 355 nm (60); ^1H NMR ($CDCl_3$, 400 MHz) δ (8*R*:*S* = 1/1) 9.04 (1H, s, 5-H), 8.65 (1H, s, 10-H), 8.37 (1H, s, 20-H), 5.64, 5.49 (each 1H, d, *J* = 21 Hz, 13^1-CH_2), 4.35 (1H, m, 18-H), 4.17 (1H, m, 17-H), 3.74 (2H, q, *J* = 7.5 Hz, 3-CH_2), 3.63 (3H, s, 17^2-$COOCH_3$), 3.59 (3H, s, 12-CH_3), 3.22 (3H, s, 2-CH_3), 2.67 (2H, m, 8-CH_2), 2.55–2.30 (4H, m, 17-CH_2CH_2), 1.89/87 (3H, s, 8-CH_3), 1.76 (3H, d, *J* = 7 Hz, 18-CH_3), 1.67 (3H, t, *J* = 7.5 Hz, 3^1-CH_3), 0.52/50 (3H, t, *J* = 7.5 Hz, 8^1-CH_3), 0.55, −1.10 (each 1H, s, NH × 2); MS (TOF) *m*/*z* 583.8, calcd for $C_{34}H_{39}N_4O_3S$: MH^+, 583.3; HRMS (FAB) *m*/*z* 583.2723, calcd for $C_{34}H_{39}N_4O_3S$: MH^+, 583.2743.

2.2.2. Methyl 7-demethyl-13^1-deoxo-8-methyl-7,13^1-dithioxo-mesopyropheophorbide-*a* (**3**)

To a solution of **2** (8*R*:*S* = 1:1, 40 mg, 69 μmol) in toluene (10 mL) was added Lawesson's reagent (60 mg, 148 μmol), then the solution was refluxed for 5 h. The reaction mixture was concentrated in vacuo. The resulting residue was purified by FCC (20% hexane/CH_2Cl_2) to give **3** in 51% yield as a 1.2:1 8-epimeric mixture: brown solid; UV–VIS–NIR (CH_2Cl_2) λ_{max} 787 (relative intensity, 100), 718 (24), 648 (13), 489 (65), 376 (32), 325 nm (61); ^1H NMR ($CDCl_3$, 400 MHz) δ (8*R*:*S* = 1.2/1) 9.61 (1H, s, 5-H), 8.72 (1H, s, 10-H), 8.31 (1H, s, 20-H), 5.63, 5.48 (each 1H, d, *J* = 22 Hz, 13^1-CH_2), 4.33 (1H, m, 18-H), 4.16 (1H, m, 17-H), 3.76 (2H, q, *J* = 8 Hz, 3-CH_2), 3.64/63 (3H, s, 17^2-$COOCH_3$), 3.61 (3H, s, 12-CH_3), 3.21 (3H, s, 2-CH_3), 2.76/78 (2H, q, *J* = 7.5 Hz, 8-CH_2), 2.55–2.30 (4H, m, 17-CH_2CH_2), 1.90/91 (3H, s, 8-CH_3), 1.77/76 (3H, d, *J* = 7 Hz, 18-CH_3), 1.70 (3H, t, *J* = 8 Hz, 3^1-CH_3), 0.21/18 (3H, t, *J* = 7.5 Hz, 8^1-CH_3), 0.68, −0.90 (each 1H, s, NH × 2); MS (TOF) *m*/*z* 598.0, calcd for $C_{34}H_{38}N_4O_2S_2$: M^+, 598.2; HRMS (FAB) *m*/*z* 599.2531, calcd for $C_{34}H_{39}N_4O_2S_2$: MH^+, 599.2514.

2.2.3. Methyl 7-demethyl-8-methyl-7-thioxo-mesopyropheophorbide-*a* (**4**)

To a chloroform (15 mL) solution of **3** (8*R*:*S* = 1.2/1, 20 mg, 34 μmol) was added a methanol solution (1.5 mL) saturated with zinc acetate dihydrate, then the solution was stirred at room temperature overnight. The reaction mixture was poured into water and washed with an aqueous 4% sodium bicarbonate solution and water. The organic layer was dried over sodium sulfate and concentrated in vacuo. The resulting residue was purified by FCC (3% diethyl ether/CH_2Cl_2) to give **4** in 26% yield as a 1.2:1 8-epimeric mixture: green solid; UV–VIS–NIR (CH_2Cl_2) λ_{max} 748 (relative intensity, 100), 709 (13), 683 (21), 618 (14), 488 (67), 466 (60), 345 (49), 317 nm (57); ^1H NMR ($CDCl_3$, 600 MHz) δ (8*R*:*S* = 1.2/1) 9.74 (1H, s, 5-H), 8.79 (1H, s, 10-H), 8.43 (1H, s, 20-H), 5.19, 5.05 (each 1H,