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Synthesis and physical properties of carbonylated chlorophyll derivatives

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ABSTRACT

Methyl pyropheophorbide-*a*, one of the chlorophyll-*a* derivatives, was modified to chlorins possessing/lacking oxo groups at the peripheral 3^1-, 8^1-, and 13^1-positions. Since the carbonyl groups were directly conjugated with the chlorin π-system in a molecule, such electron-withdrawing groups affected visible absorption and fluorescence emission spectra, emission efficiencies, and emission lifetimes as well as oxidation potentials of the semi-synthetic chlorophyll derivatives in a solution. The substitution effect was dependent on the connecting positions.

1. Introduction

In natural systems, various chlorophyllous molecules are found[1–5] and also their biosynthetic intermediates[6] and degradates with a cyclic tetrapyrrole skeleton[7] are observed. Especially, a large amount of chlorophyll-*a* (Chl-*a*) is available in oxygenic phototrophs including plants and algae. Chl-*a* molecule possesses three carbonyl groups in peripheral substituents of the tetrapyrrole, 13-keto- and 13^2,17^2-ester-carbonyl groups (see the left drawing of Fig. 1). The 13-carbonyl substituent is directly conjugated with the π-system of cyclic tetrapyrroles and largely affects the photophysical properties of all the natural chlorophyllous pigments. Except the 13-C=O group, several carbonyl moieties are π-conjugated with porphyrin, chlorin (17,18-dihydroporphyrin), and bacteriochlorin (7,8,17,18-tetrahydroporphyrin) skeletons at the other positions of natural occurring Chl and bacteriochlorophyll (BChl) molecules: 2-CHO (Chl-*f*), 3-CHO (Chl-*d* and its 13^2-epimeric Chl-*d*′), 3-COMe (BChls-*a*/*b* and their demetalated BPhes-*a*/*b*), 7-CHO (Chl-*b* and BChls-*e*/*f*), 7-COOMe (Chl-c_3).[1,8] Substitution of a methyl group with a formyl group at the 2-position bathochromically shifted the longest wavelength (Q_y) absorption maxima of the monomeric state in a solution: 661 for Chl-*a* with 2-CH_3 to 695 nm for Chl-*f* with 2-CHO in diethyl ether.[8,9] Introduction of the 3-formyl and acetyl groups similarly moved Q_y maxima to longer wavelengths: 661 for Chl-*a* (3-vinyl) to 686 nm for Chl-*d* (3-formyl) and 767 for BChl-*g* (3-vinyl) to 795 nm BChl-*b* (3-acetyl) in Et_2O.[2,3] In contrast, alteration of a methyl to formyl group at the 7-position induced a blue shift of monomeric Q_y peak positions: 661 for Chl-*a* (7-CH_3) to 642 nm for Chl-*b* (7-CHO) in Et_2O.[2–4] Such carbonylation at the β-positions of A- and B-rings thus moved singlet excited states of monomeric (B)Chl molecules to lower and higher levels, respectively. Additionally, the π-conjugation degree of the carbonyl groups with tetrapyrrole skeletons affected Q_y maxima as follows. The 3-acetyl group of BChl-*a* was rotated

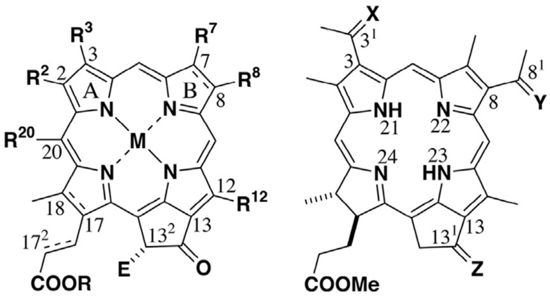

Fig. 1. Molecular structures of naturally occurring chlorophylls (R^2=Me, CHO; R^3=CH=CH_2, CHO, COMe; R^7=Me, CHO, COOMe; R^8=Et, other alkyl groups; R^{12}=Me, Et; E=H, COOMe; R=H, farnesyl, phytyl; R^{20}=H, Me; M=2H, Mg) (left) and methyl (3^1-oxo-, 8^1-oxo- and/or 13^1-deoxo-)mesopyropheophorbides-*a* **1a**–**8a** (X, Y, Z=H_2 or O) (right) prepared by modifying Chl-*a* (R^2=R^7=R^{12}=Me, R^3=CH=CH_2, R^8=Et, E=COOMe, R=phytyl, R^{20}=H, and M=Mg in the right drawing).

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through the C3–C3^1 single bond from the tetrapyrrole π-plane to disconnect their conjugation, leading to blue shifts of their Q_y maxima in FMO protein, one of the peripheral antenna systems of green sulfur photosynthetic bacteria.[10,11] Hydrogen bond of the carbonyl group with its environmental moieties including peptides and water molecules regulated the singlet excited energy as well.[10]

Chl derivatives possessing directly π-conjugated carbonyl groups have been reported previously.[3] The semi-synthetic Chls carbonylated at the 2-,[9] 3-,[12,13] 7-,[14] 8-,[13,15] 12-,[16] and 20-positions[17] gave different visible absorption spectra as mentioned above and also showed their specific reactivities.[15,18] Here we report on the synthesis of Chl derivatives **1a**–**8a** possessing or lacking carbonyl groups at the 3-, 8-, and 13-positions (see the right drawing of Fig. 1) by modifying natural Chl-*a* and discuss the substitution effect on their optical and electrochemical properties in dichloromethane.

2. Results and discussion

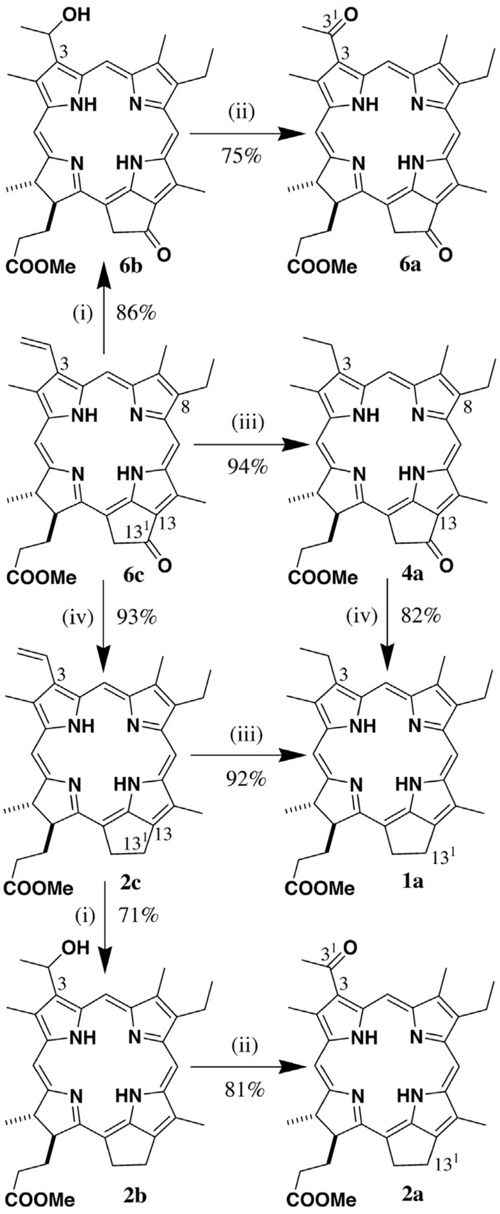
2.1. Synthesis of methyl pyropheophorbides

Chl-*a* was extracted from commercially available spirulina powder and modified to methyl pyropheophorbide-*a* (**6c**) according to reported procedures.[19,20] As shown in Scheme 1, the 3-vinyl group of **6c** was catalytically hydrogenated to give methyl meso-pyropheophorbide-*a* (**4a**)[19] in an excellent yield (94%) and its 13-keto-carbonyl group was fully reduced to afford methyl 13^1-deoxo-mesopyropheophorbide-*a* (**1a**) in a very good yield (82%).[21] Alternatively, the 13-carbonyl group of **6c** was first transformed into the 13-methylene group as in **2c** (93%) and then the 3-vinyl group was converted to the 3-ethyl group as in **1a** (92%). The synthetic route to **1a** from **6c** through **2c** was slightly favorable over that via **4a**, because the total yield of the former (86%) was larger than that of the latter (77%).

The 3-vinyl group of **6c** was hydrated to afford methyl bacteriopheophorbide-*d* (**6b**) in a very good yield (86%)[20] and the resulting 1-hydroxyethyl group was oxidized to the 3-acetyl group as in **6a** (75%).[21] Similarly, **2c** was converted to **2a** through **2b** and the yields for the hydration (71%) and oxidation (81%) were comparable to those in the above transformation of **6c** to **6b** and of **6b** to **6a**. It is noted that the 13^1-oxo group did not largely affect the hydrogenation (13^1-deoxo-**2c**/13^1-oxo-**6c** to **1a**/**4a**), hydration (**2c**/**6c** to **2b**/**6b**), and oxidation (**2b**/**6b** to **2a**/**6a**) of the 3-substituents.

Oxidation of the C7=C8 double bond in **4a** gave *cis*-diol **4d** (69%) as shown in Scheme 2.[22,23] 7,8-Dihydroxy-bacteriochlorin **4d** in THF was treated with an aqueous hydrogen chloride solution at room temperature to afford the mono-dehydrated product. The product was a mixture of minor 7^1-hydroxy- **7e** and major 8^1-hydroxy-chlorins **7b** and separated by flash column chromatography (FCC) to yield a pure sample of **7b** (51%).[15] The acidic dehydration proceeded through cationic species, so secondary alcohol **7b** was obtained in more quantity than primary alcohol **7e**, which was consistent with previous results.[24] Desired alcohol **7b** was synthesized by the other route from **4d** as follows. Double dehydration of **4d** gave 8-vinyl-chlorin **7c** (60%) and the 8-vinyl group was hydrated to **7b** (50%). The total yield of the two steps in **4d** to **7b** via **7c** was 30% and less than the yield of the direct conversion of **4d** to **7b**, but the tedious and careful FCC separation of regioisomeric alcohols requisite for the latter could be avoided in the former. A large amount of **7b** was prepared from **4d** by the two-step procedures. Finally, the 1-hydroxyethyl group of **7b** was oxidized to 8-acetyl group as in **7a** (59%).[15]

Similar to the synthesis of **7a** from **4a**, the 8-ethyl group of 3-acetyl-chlorin **6a** was converted to the 8-acetyl group as in **8a**[15] (see Scheme 3). The yields for the single and double dehydration of *cis*-diol **6d** (38 and 49%) were less than those in **4d** (51 and 60%). The suppression was ascribable to the presence of the electron-withdrawing acetyl group at the 3-position in **6d** instead of the 3-ethyl group in **4d**, since the acidic dehydration of *cis*-diols **4d**/**6d** was performed through cationic species (vide supra). Because major mono-dehydrated product **8b** could not be separated from minor product **8e** by FCC, HPLC was necessary for isolation of desired secondary alcohol **8b**.



Scheme 1. Synthesis of methyl (3^1-oxo- and/or 13^1-deoxo-)mesopyropheophorbides-*a* **1a**/**2a**/**4a**/**6a** by modifying methyl pyropheophorbide-*a* (**6c**): (i) HBr/AcOH, H_2O, CH_2N_2/Et_2O; (ii) $MeN(O)(CH_2CH_2)_2O–Pr_4NRuO_4/CH_2Cl_2$; (iii) H_2, Pd–C/Me_2CO–THF; (iv) $NaBH_4$–TFA/CH_2Cl_2.

Synthesis of **5a** by transformation of the 8-ethyl group in **2a** to the 8-acetyl group was examined according to the above procedures (Scheme 4). First, *cis*-diol **2d** prepared by the oxidation of **2a** (61%)[22] was treated with hydrogen chloride in aqueous THF to give the mono-dehydrated product. The product was a mixture of 7^1-hydroxy- **5e** and 8^1-hydroxy-chlorins **5b**. In the mixture, primary alcohol **5e** was dominant and desired secondary alcohol **5b** was produced in a trace amount. The regioselectivity was the reverse of those in mono-dehydration of *cis*-diols **4d** and **6d** possessing the 13^1-oxo moiety. As a result, the 13-carbonyl group controlled the regioselectivity in the mono-dehydration, although the 3-carbonyl group did not. It is noteworthy that a 7-