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Synthesis of amino-analogs of bacteriochlorophyll-*d* and their self-aggregation in an aqueous micelle solution



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ABSTRACT

Zinc methyl 3-aminomethyl- and 3-(1-aminoethyl)-pyropheophorbides-*a* were prepared by modifying naturally occurring chlorophyll-*a*. The synthetic amino-analogs of bacteriochlorophyll-*d* self-aggregated in an aqueous micelle solution to give large oligomers with red-shifted and broadened electronic absorption bands. The spectra of these self-aggregates were similar to those of bacteriochlorophyll self-aggregates in the main light-harvesting antennas of green photosynthetic bacteria. The 3¹-amino groups were alternative to the 3¹-hydroxy groups in natural bacteriochlorophylls-*c/d/e/f*.

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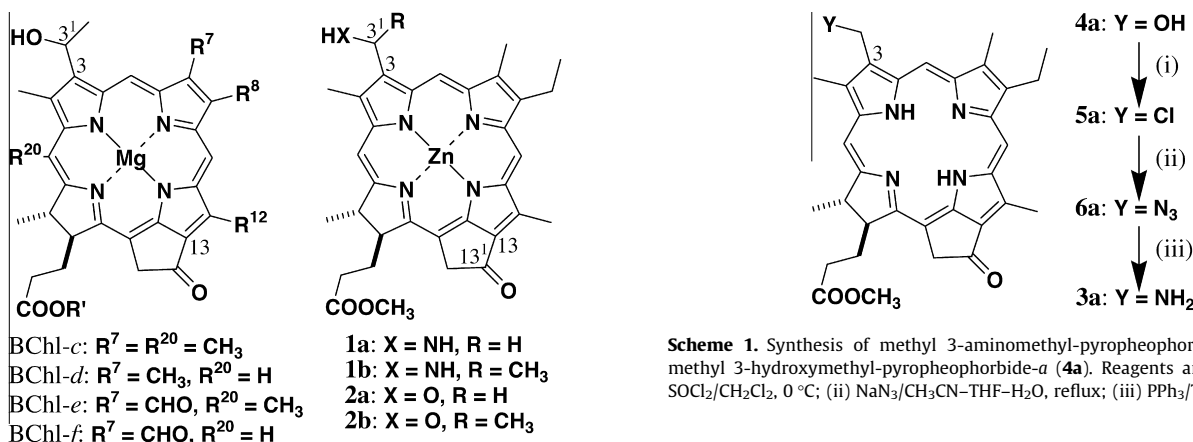
Bacteriochlorophylls (BChls)-*c*, *d*, *e*, and *f* are naturally occurring pigments and found solely in main light-harvesting antenna systems of green photosynthetic bacteria, called chlorosomes.¹ Their molecular structures are in part different from that of chlorophyll-*a*, especially, the presence of 1-hydroxyethyl group at the 3-position and the absence of methoxycarbonyl group at the 13²-position (see the left drawings of Fig. 1).² Such a structural modification enhances the intermolecularly interacting abilities of the 3/13-substituents in the above BChl molecules. They specifically self-aggregate in a chlorosome to form large oligomers in a J-type fashion. The supramolecules are constructed by coordination of the 3¹-O to Mg, hydrogen-bond of 3¹-O—H with 13-C=O, and π - π interaction of the composite chlorin systems (see Graphic Abstract). As the synthetic models, zinc 3¹-hydroxy-13¹-oxo-chlorins including **2a/b** (right upper drawing of Fig. 1) were prepared and their self-aggregation in hydrophobic environments was investigated by various spectroscopies.^{3,4} The 3¹-methoxy analogs of **2a** were synthesized as alternative models and did self-aggregate similarly under specific conditions in spite of lacking a hydrogen-bond donating part.⁵ Some zinc 3¹-amino-substituted 13¹-oxo-chlorins also formed their small and/or large aggregates in nonpolar organic solvents.^{6,7} Here zinc bacteriopheophorbide-*d* analogs **1a–c** bearing an amino group in the 3-substituent (right drawing of Fig. 1) were prepared and their self-aggregation in an aqueous micelle solution was examined.

According to reported procedures,³ methyl 3-hydroxymethyl-pyropheophorbide-*a* (**4a**) was prepared by modifying naturally occurring chlorophyll-*a* (see Scheme 1). The reaction of alcohol **4a** with thionyl chloride gave chloride **5a** [step (i) of Scheme 1],⁸ which was converted to azide **6a**⁹ by treatment with sodium azide [step (ii)] in an excellent yield.¹⁰ Since chloride **5a** was chemically reactive and fairly unstable during the purification, it was used for the following azidation without isolation and just after evaporation of all the volatile components in the chlorination reaction mixture. The present one-pot procedures were simpler and afforded a higher yield than the previous stepwise ones: 94% > 71% (=83%⁹ × 86%¹⁰) for the total yields from **4a** to **6a** via **5a**. Hydrogenation of azide **6a** under standard conditions (Pd/C in acetone)⁸ was examined but in vain. Using platinum dioxide as the catalyst was effective for the hydrogenation but the resulting amine **3a** was further condensed with acetone as the solvent to give the corresponding imine, which was further hydrogenated to yield undesired 3-(isopropylamino)methyl-chlorin as the sole product. To avoid the further reactions, THF was used for the solvent and **3a** was isolated in at most 30% yield. Staudinger reaction of azide **6a** with triphenylphosphine in aqueous THF afforded amine **3a** in an improved 64% yield [step (iii)]. Free base **3a** was zinc-metallated to give zinc complex **1a** in a 95% isolated yield [step (iv) of Scheme 2].

The 3¹-hydroxy group of methyl bacteriopheophorbide-*d* (**4b**)⁴ was transformed into the amino group of **3b** according to the above procedures except the following points (see Schemes 2 and S1). The secondary chloride (3-CHClCH₃) was more reactive than the primary chloride **5a**, so the corresponding triflate

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Scheme 1. Synthesis of methyl 3-aminomethyl-pyrropephorbide-a (**3a**) from methyl 3-hydroxymethyl-pyrropephorbide-a (**4a**). Reagents and conditions: (i) SOCl₂/CH₂Cl₂, 0 °C; (ii) NaN₃/CH₃CN-THF-H₂O, reflux; (iii) PPh₃/THF-H₂O, 50 °C.

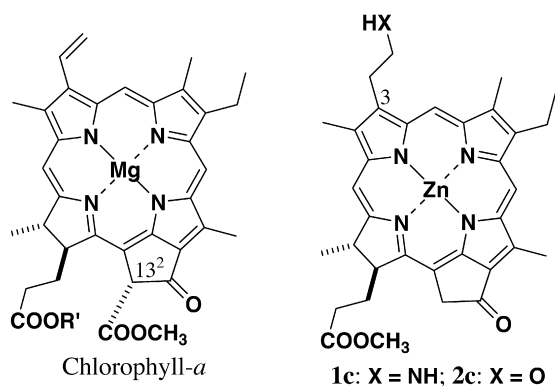


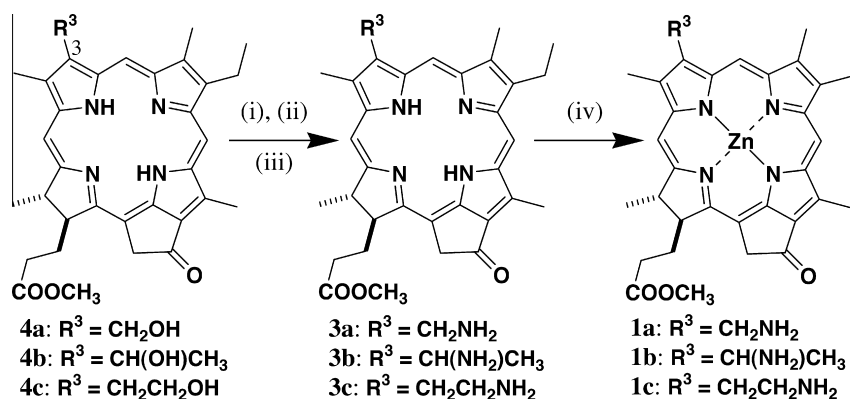
Figure 1. Molecular structures of naturally occurring chlorophylls (left) and their synthetic models bearing an amino **1a–c** or hydroxy group **2a–c** (right): R⁸ = CH₂, CH₃, CH₂CH₂CH₃, CH₂CH(CH₃)₂, or CH₂C(CH₃)₃; R¹² = CH₃ or CH₂CH₃.

prepared by treatment with trifluoroacetic anhydride was used for azidation. The resulting secondary azide was less reactive due to the steric hindrance and reduced to amine **3b** for a longer reaction time than the primary azide **6a**: 1 day (for **3b**) > 1 h (for **3a**). In contrast, the other amine **3c** bearing a primary alkyl group was prepared from primary alcohol **4c**¹¹ by the same procedures as in **4a** to **3a** (Scheme 2). Both **3b/c** were zinc-inserted to give **1b/c** by step (iv) of Scheme 2. Synthetic amino-analog **1b** of secondary alcohol **2b** was a 3¹-epimeric mixture (1:1), which was used for the following measurements.

Zinc 3-aminomethyl-chlorophyll derivative **1a** gave sharp visible absorption and small circular dichroism (CD) spectra in THF (broken blue lines of Fig. 2A). Compared with the previous results (see also the broken blue lines of Fig. 2D for **2a**),³ the observed

spectra clearly indicate that zinc complex **1a** was coordinated with a THF molecule as its axial ligand to form the monomeric state in THF. In an aqueous phosphate buffer solution (pH = 6.86) containing 1%(v/v) THF and 0.025%(wt/v) Triton X-100,¹² **1a** showed red-shifted and broadened electronic absorption bands at 724 and 455 nm with small residual monomeric peaks at 659 and 432 nm (solid red line in the upper spectra of Fig. 2A); the former and latter were called Qy and Soret bands, respectively. In the measurements, the nearly neutral buffer solution was used to avoid the protonation of the 3¹-amino group. The absorbance of Qy maximum in the micellar solution was about twice larger than the Soret intensity, while the Qy absorbance in THF was smaller than the Soret. These spectral features indicated that **1a** in the aqueous micelle self-aggregated in a J-type fashion similarly as in natural chlorosomes¹ and their model systems prepared by self-aggregation of **2a/b**^{3,4} (see also the solid red line in the upper spectra of Fig. 2D for **2a**). Larger S-shaped CD bands were observed in red-shifted Qy and Soret regions (solid red line in the lower spectra of Fig. 2A), supporting the chlorosomal self-aggregation of **1a** in the micelle. Therefore, the amino group at the 3¹-position of **1a** was effective for the J-type self-aggregation as well as the 3¹-hydroxy group of **2a**. The Soret maximum of self-aggregated **1a** was situated at 455 nm and the value was larger than that of self-aggregated **2a** (450 nm). The bathochromic shift was reverse to the hypsochromic shift in Qy maxima (vide supra). Moreover, the CD shapes of self-aggregated **1a** were roughly the reverse of those in **2a**. The stacking direction of composite pigments in supramolecular structures might be slightly altered in spite of using the same motif as the specific bonding: Zn...N–H...O=C for **1a** and Zn...O–H...O=C for **2a**.

Conversion of the self-aggregates to monomer of **1a** was examined by addition of Triton X-100 to the micellar solution.



Scheme 2. Synthesis of zinc methyl 3¹- or 3²-amino-pyrropephorbide-a derivatives **1a–c** from methyl bacteriopheophorbide-d analogs **4a–c**. Reagents and conditions: (i) SOCl₂ (for **a** and **c**) or (CF₃CO)₂O (for **b**)/CH₂Cl₂, 0 °C; (ii) NaN₃/CH₃CN-THF-H₂O, reflux; (iii) PPh₃/THF-H₂O, 50 °C; (iv) Zn(OAc)₂·2H₂O/CH₃OH-CH₂Cl₂, rt.

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