



Synthesis of zinc 20-substituted bacteriochlorophyll-*d* analogs and their self-aggregation



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ABSTRACT

Zinc complexes of methyl 3¹-demethyl-bacteriopheophorbides-*d* possessing a 2-(un)substituted ethynyl or ethenyl group at the 20-position were prepared through palladium-catalyzed cross-coupling of their 20-bromide with the corresponding alkyne or alkene. The synthetic zinc 20-substituted 3-hydroxy-methyl-13¹-oxo-chlorins self-aggregated in an aqueous micellar solution to give similar large oligomers as self-aggregates of bacteriochlorophylls in the core part of the main light-harvesting antenna of photosynthetic green bacteria. The zinc 20-ethynyl-chlorin fully gave the self-aggregates, but its 20²-substitution disturbed the self-aggregation. The 20-(2-phenyl)ethenyl moieties induced the formation of relatively smaller oligomers as well as residual monomers due to their steric bulkiness.

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Self-aggregates of pigments have attracted much attention in the fields of biological and medicinal sciences as well as materials science and physics.¹ Cyclic tetrapyrroles self-aggregate in some natural organisms to give biological functions: especially, self-aggregates of a heme (an iron porphyrin) in hemazoin² and of chlorophylls (magnesium dihydroporphyrins = chlorins) in chlorosomes (main light-harvesting antenna systems of green photosynthetic bacteria).³ In the latter, a large amount of bacteriochlorophyll(BChl)-*c*, *d*, *e*, or *f* molecules specifically interact to form highly ordered supramolecules with efficiently absorbing sunlight, migrating the excited energy, and transferring it to other pigments. BChl-*c* is the 20-methyl analog of BChl-*d* (see left drawing of Fig. 1), while BChl-*e* is the 20-methylated BChl-*f*. In their monomeric and J-aggregated states, the substitution with a methyl group at the 20-position affected light-absorption bands and singlet-excited energy levels: red-shifts of the absorption maxima and decrease of the energy levels by the 20-methylation.⁴ As the model of naturally occurring BChl-*d*, zinc 3-hydroxymethyl-13¹-oxo-chlorin **1f** (in right drawing of Fig. 1) was already prepared where the 3¹-methyl group was removed, the central magnesium was replaced by zinc, and the long hydrocarbon chain in the 17-propionate residue was substituted with a methyl group.⁵ The synthetic compound **1f** readily self-aggregated in non-polar organic or aqueous organic solvents, in aqueous micelles, and in the solid states to give similar supramolecules as in chlorosomes. The halogenation at the 20-position of **1f** (R = F, Cl, and Br) was reported to disturb the

planarity of chlorin π -systems and gradually change optical properties similarly to the 20-methylation in BChl-*d* to *c* (vide supra).⁶ Other than the above simple 20-substituents has not yet been examined for chlorosome-like self-aggregation.

Here we describe the synthesis of zinc methyl 20-substituted 3¹-demethyl-bacteriopheophorbides-*d* by palladium-catalyzed cross-coupling and their self-aggregation in an aqueous micellar solution. The newly introduced 20-substituents ($-\text{C}\equiv\text{C}-\text{R}'$ and $-\text{CH}=\text{CH}-\text{R}'$) altered the optical properties in THF (monomer) and an aqueous Triton X-100 solution (J-aggregates), which is

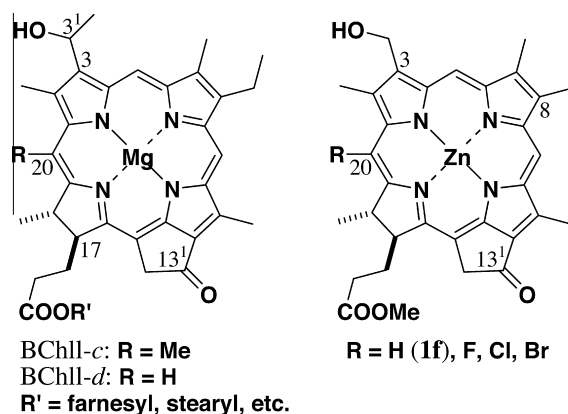


Figure 1. Molecular structures of bacteriochlorophylls(BChls)-*c* and *d* (simplest homologs) in the main light-harvesting antenna systems of green photosynthetic bacteria (left) and their synthetic models (right).

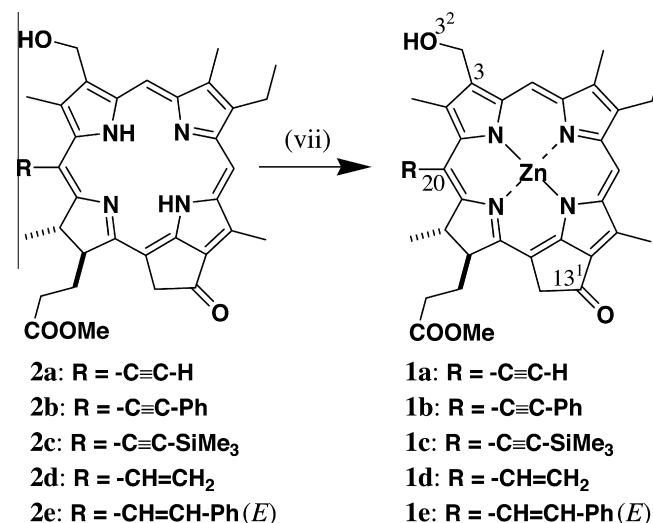
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discussed by focusing on their electronic and steric factors. The present investigation first clarified the kind of 20-substituents tolerant of the formation of such self-aggregates.

Methyl 3-devinyl-3-hydroxymethyl-pyropheophorbide-*a* (**2f**), one of the chlorophyll-*a* derivatives, was reacted with pyridinium tribromide in dichloromethane⁷ to give the corresponding 20-bromo-chlorin **2g**⁶ in an 85% isolated yield [step (i) in Scheme 1]. Under standard copper-free Sonogashira-coupling conditions [step (ii)],⁸ bromide **2g** was treated with trimethylsilylacetylene to afford desired 20-trimethylsilylethynyl-chlorin **2c** and undesired debromo-chlorin **2f**. Additionally, **2c** was over-reacted with $\text{Me}_3\text{Si}-\text{C}\equiv\text{C}-\text{H}$ ⁹ to be transformed into ene-yne product **2h**. To avoid the mixed products, Migita-Kosugi–Stille coupling⁷ of **2g** with tributyl(trimethylsilylethynyl)stannane was examined and trimethylsilyl-protected product **2c** was successfully isolated in a 62% yield [step (iii)]. The resulting compound **2c** was treated with tetrabutylammonium fluoride in dichloromethane to afford 20-ethynyl-chlorin **2a** in a 64% yield [step (iv)]. A similar cross-coupling reaction of **2g** with tributyl(phenylethynyl)stannane gave 20-phenylethynyl-chlorin **2b** in a 78% yield.

Under the same cross-coupling conditions [step (iii)], 20-bromo-chlorin **2g** was reacted with tributyl(vinyl)stannane⁷ to give a mixture of 20-vinyl-chlorin **2d** (Stille-coupling product) and 20-tributylethynyl-chlorin **2i** (Heck-reaction product). The mixture was treated with silica gel in dichloromethane⁷ to afford **2d** (57%) as an isolable product [step (v)] due to an effective destannylation of **2i** to **2d** on its solid surface. Mizoroki–Heck reaction of **2g** with styrene [step (vi)]¹⁰ gave 20-phenylethynyl-chlorin **2e** (40%). The 1,2-disubstituted ethylene product was the sole *E*-isomer from its ¹H NMR spectral analysis: $J(\text{C}20^1\text{H}-\text{C}20^2\text{H}) = 16 \text{ Hz}$. It is noteworthy that no palladium chlorins were observed

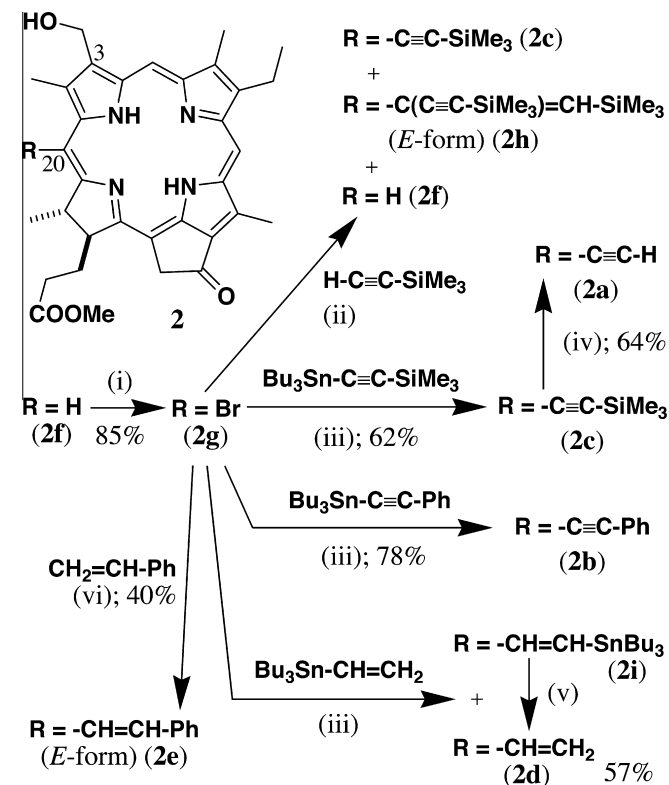


Scheme 2. Zinc-metallation of free bases **2a–e** to zinc methyl 20-substituted 3-hydroxymethyl-pyropheophorbides-*a* **1a–e**. Reagents and conditions: (vii) $\text{Zn}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}/\text{MeOH}-\text{CH}_2\text{Cl}_2$, rt.

in the reaction mixtures after the above Pd-catalyzed cross-couplings. Free bases **2a–e** were transformed to zinc complexes **1a–e** under standard conditions¹¹ [step (vii) in Scheme 2]. All the zinc chlorins were purified by reverse-phase HPLC (see [Electronic Supporting material](#)) and used for the following optical measurements.

In THF, zinc 20-ethynyl-chlorin **1a** showed two sharp electronic absorption bands at 659 and 429 nm (see broken line of upper spectra of Fig. 2A), called Qy and Soret bands, respectively.¹² In the same solution, negative and positive small CD peaks were observed at the Qy and Soret maxima, respectively (see broken line in lower spectra of Fig. 2A). These results showed that zinc complex **1a** in the diluted solution was a monomeric species axially coordinated with a THF molecule. Its concentrated THF solution was diluted 99-fold with water in the presence of Triton X-100, one of the nonionic detergents, to give red-shifted and broadened absorption bands (see solid line of upper spectra of Fig. 2A). Especially, the Qy band moved to a longer wavelength from 659 to 776 nm and the full width at its half maximum (FWHM) increased from 320 to 590 cm^{-1} . The red-shift value was 2290 cm^{-1} (see Table 1) and the broadening ratio was 1.8 times. These changes are similar to the J-type self-aggregation of **1f** reported previously:⁵ 647 → 743 nm (2000 cm^{-1}) and 330 → 530 cm^{-1} (1.6 times). Therefore, **1a** self-aggregated under a hydrophobic environment inside the aqueous Triton X-100 micelle to form large oligomers with a J-type fashion. The self-aggregates of **1a** would be constructed by a motif similar to those of **1f**:⁵ $\text{Zn} \cdots \text{O}3^2-\text{H} \cdots \text{O}=\text{C}13^1$. Compared with the red-shift values of **1a/f**, the 20-ethynyl group did not disturb the J-aggregation, but the interaction of chlorin π -systems was enhanced in the supramolecule. This is ascribable to an increase of π -conjugation in **1a**, which is consistent with the self-aggregation of zinc 8-substituted chlorin reported earlier.¹³ The large CD bands at the red-shifted regions supported such J-aggregation of **1a** (see lower spectra of Fig. 2A), since a similar CD spectral change was previously reported in that of **1f**.⁵

The substitution of a phenyl group at the 20²-position of **1a** as in **1b** moved the Qy and Soret peaks in THF to longer wavelengths by 6 nm with little changes in their spectral shapes: 659 and 429 → 665 and 435 nm (broken lines of upper spectra of Fig. 2A and B). The bathochromic shifts are ascribable to the π -conjugation of the phenyl group with a chlorin moiety through an acetylene spacer in a molecule. Its energy minimized molecular models⁶



Scheme 1. Synthesis of methyl 20-substituted 3-hydroxymethyl-pyropheophorbides-*a* **2a–e**. Reagents and conditions: (i) $\text{C}_5\text{H}_5\text{NH}^+\text{Br}_3^-/\text{CH}_2\text{Cl}_2$, rt; (ii) $\text{Pd}_2(\text{dba})_3$, (*o*-tolyl)₃P, $\text{Et}_3\text{N}/\text{dry DMF}$, rt; (iii) $\text{Pd}(\text{PPh}_3)_4/\text{dry THF}$, reflux; (iv) $(n\text{-Bu})_4\text{NF}/\text{THF}-\text{CH}_2\text{Cl}_2$, rt; (v) $\text{SiO}_2/\text{CH}_2\text{Cl}_2$, reflux; (vi) $\text{Pd}(\text{OAc})_2$, 2-(*t*-Bu)₂P-biphenyl, $\text{K}_2\text{CO}_3/\text{DMF}-\text{toluene}$, 90 °C. All the synthetic procedures are shown in [Electronic Supporting material](#).

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