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Synthesis of 20-iodochlorophyll derivatives and their properties including reactivity, electronic absorption, and self-aggregation

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ABSTRACT

Methyl 20-iodopyropheophorbides-*a* possessing several substituents at the 3-position were prepared by treatment of the corresponding 20-unsubstituted chlorophyll-*a* derivatives with iodine and [bis(trifluoroacetoxy)iodo]benzene in chloroform and water at room temperature. The sterically demanding 20-iodination was clean, efficient, and regioselective without alteration of the 3-substituents, and also highly reproducible. The resulting 20-iodides were so reactive that they were readily transformed into 20-acetylchlorin (Pd-catalyzed cross-coupling) and 20-unsubstituted chlorin (acidic deiodination). Electronic absorption spectra in dichloromethane showed that the 20-iodination shifted the maxima to longer wavelengths in their monomeric states. Zinc complexes of 3^1-hydroxy-20-iodo-13^1-oxochlorins self-aggregated in non-polar organic solvents to give red-shifted and broadened absorption bands, similarly as in the corresponding 20-unsubstituted molecules, which are good models of the main light-harvesting antenna systems in photosynthetic green bacteria.

1. Introduction

Most photosynthetically active chlorophyllous pigments are porphyrinoids possessing a substituent at only one of the four *meso*-positions, the 15-position.[1] In contrast, bacteriochlorophylls-*c* and *e* (BChls-*c* and *e*) are additionally substituted with a methyl group at another *meso*-position, the 20-position (left drawing of Fig. 1). In diethyl ether, 20-methylated BChls-*c* and *e* have electronic absorption bands at longer wavelengths than the corresponding 20-unsubstituted BChls-*d* and *f*, respectively.[2] The red-shifted absorption maxima in their monomeric states are primarily due to the steric effect of the 20-methyl group, which interacts with the neighboring 2- and 18-methyl groups to distort the chlorin π-system.[3] In green photosynthetic bacteria, BChls-*c*, *d*, *e*, and *f* self-assembled to form large J-aggregates and gave more bathochromically shifted absorption bands than their monomeric bands described above. Such J-aggregates efficiently absorb dim light and the harvested light energy is transferred to nearby BChl-*a* pigments. Similar to the monomeric states, oligomeric BChls-*c*/*e* in natural cells showed more red-shifted maxima than the corresponding BChls-*d*/*f*, so the former are more effective for absorbing longer wavelength light and transferring the energy to BChl-*a* than the latter.[4,5] The 20-methylation is thus useful for some bacteria living in natural environments.

A variety of semi-synthetic 20-substituted Chl derivatives are available in the literature.[6,7] For example, methyl mesopyropheophorbide-*a* (**1b**) derived from naturally occurring Chl-*a* was modified to its 20-substituted compounds (central drawing of Fig. 1): R^{20}=alkyl,[8,9] alkenyl,[9] alkynyl,[9–11] aryl,[8,12,13] acyl,[9] cyano,[14] nitro,[14,15] halogen substituents,[9,16–18] and so on.

The iodination of porphyrinoids has been reported in some manuscripts. Zinc complexes of 5,15-diarylporphyrins (none of β-substitution and half of *meso*-substitution, M=Zn and R^{10}=R^{20}=H in right drawing of Fig. 1) in chloroform were treated with iodine in the presence of silver hexafluoride and pyridine at room temperature to give their *meso*-mono- and di-iodinated products as major and minor products, respectively.[19] The reaction of 5,10,15-triarylporphyrin free bases (M=H_2, R^{10}=Ar, and R^{20}=H in right drawing of Fig. 1) with iodine and (difluoroiodo)benzene ($PhIF_2$, one of the hypervalent iodine reagents) in dichloromethane at room temperature afforded their 20-iodo-products.[20] A mixture of

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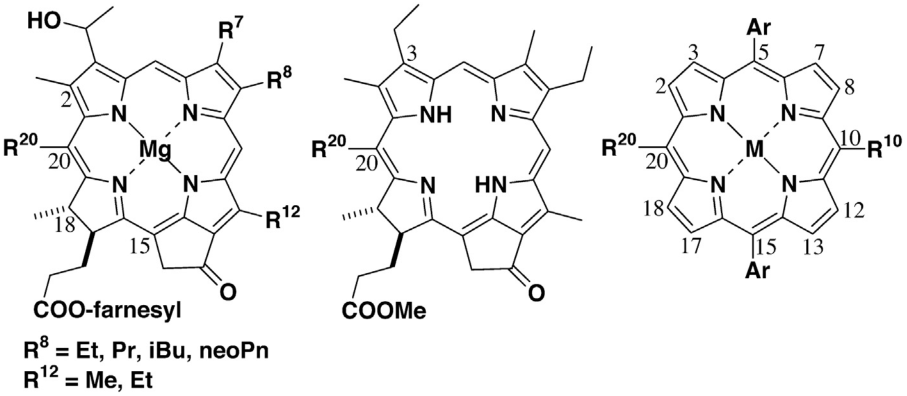

Fig. 1. Molecular structures of naturally occurring BChls-*c* (R^7=R^{20}=Me), *d* (R^7=Me, R^{20}=H), *e* (R^7=CHO, R^{20}=Me), and *f* (R^7=CHO, R^{20}=H) (left), methyl 20-(un)substituted mesopyropheophorbides-*a* prepared by modifying Chl-*a* (center, R^{20}=H for **1b**), and synthetic *meso*-substituted porphyrinoids (right).

iodine and [bis(trifluoroacetoxy)iodo]benzene (BTI), $PhI(OCOCF_3)_2$, is known to be a convenient electrophilic iodinating reagent for aromatic compounds.[21] The iodination of 5,15-diphenylporphyrin with I_2 and BTI in $CHCl_3$ at room temperature gave *meso*-mono-(major) and β,*meso*-disubstituted products (minor).[22] The first iodination occurred at the *meso*-position and the second proceeded at the β-position, and the selectivity was confirmed by the β-iodination of 5,10,15-triarylporphyrins with I_2 and BTI.[23] In the presence of pyridine, the reaction of a 5,15-diarylporphyrin with I_2 and BTI in $CHCl_3$ at room temperature gave predominantly its *meso*,*meso*-diiodo-product.[24] It is noted that the β- or *meso*-bromo-atom in porphyrins was substituted with an iodo-atom to yield the corresponding iodoporphyrins.[25,26]

Electrophilic iodination at the *meso*-position of 2,3,7,8,12,13,17,18-octaethylporphyrin failed when treated with I_2 and BTI.[22,27] The inaccessibility is due to the sterically demanding iodine atom and the steric hindrance around the *meso*-position near the two ethyl groups. Chlorin chromophores possessing the C17–C18 single bond showed a high reactivity at the 15- and 20-positions, so some β-substituted chlorin compounds were examined as substrates for iodination. A 2-unsubstituted and 18-substituted chlorin in $CHCl_3$ was iodinated at the 20-position by I_2 and BTI in the presence of pyridine at room temperature.[28] The iodination of a few chlorins (pyropheophorbides and purpurimides) possessing substituents at 2-, 15-, and 18-positions was applied by either I_2 and BTI or *N*-iodosuccinimide and trifluoroacetic acid in $CHCl_3$, but their 20-iodochlorins were problematically[18,29,30] or less produced.[31]

Here we report efficient synthesis of methyl 20-iodopyropheophorbides possessing several substituents at the 3-position with a high reproducibility. We discuss their chemical reactivities and iodo-substitution effect on electronic absorption bands in monomeric and self-aggregated states.

2. Results and discussion

2.1. Synthesis of methyl 20-iodopyropheophorbides

Methyl mesopyropheophorbide-*a* (**1b**), one of the chlorophyll-*a* derivatives, was used as a substrate for 20-iodination, because **1b** had an ethyl group at the 3-position instead of the reactive 3-vinyl group in methyl pyropheophorbide-*a* (**1a**) (see Scheme 1). Treatment of **1b** with I_2 and BTI in $CHCl_3$ at room temperature gave a complex reaction mixture. After its careful purification with flash column chromatography (FCC) on silica gel, one product was separated and analyzed by ^1H NMR, MS, and visible spectroscopy. The isolated product gave no proton signal at the 20-position, the mass peaks expected for the singly iodinated molecule at m/z=676 [=550 (**1b**)+127 (I)−1 (H)], and red-shifted absorption maxima: 410/656 (**1b**)→418/670 nm in CH_2Cl_2 (see also Section 2.3). The obtained spectral data indicated that the product was 20-iodinated compound **2b**. The isolated yield fluctuated in each reaction and varied from nearly 0 to about 50%. To improve the reaction, strictly dry conditions were applied (especially, use of anhydrous chloroform), but the fluctuation continued. When wet conditions (addition of water) were examined reversely, the desired product was always obtained and the yield increased. Reaction of **1b** (10 μmol) with I_2 (10 μmol) and BTI (12.5 μmol) in $CHCl_3$ (10 ml) and H_2O (2 ml) at room temperature for 30 min gave **2b** in 92% yield after FCC. The aqueous biphasic reaction was effective for the 20-iodination.

The 3^1-hydroxy-substituted compound of **1b**, methyl bacteriopheophorbide-*d* (**1c**), was converted to its 20-iodinated product **2c** by the same procedures as in **1b**→**2b** (vide supra). The reaction time for full consumption of **1c** (1 h) was double that for **1b** and the yield of **2c** (90%) was comparable to that of **2b**. Similarly, **1d** possessing an acetyl group at the 3-position was iodinated for 3 h to give **2d** in 81% yield. The slight decrease of the yield was ascribable to less electrophilic reactivity at the 20-position of **1d** bearing the electron-withdrawing 3-acetyl group. The reaction times for consumption of all the starting materials **1b**–**d** were dependent on the 3-substituents and increased in the order of **1b** ($3\text{-}CH_2CH_3$)<**1c** [$3\text{-}CH(OH)CH_3$]<**1d** ($3\text{-}COCH_3$). Electron-withdrawing groups at the 3-position suppressed the electrophilic iodination at the 20-position: group electronegativity=2.48 (CH_2CH_3)<2.60 [$CH(OH)CH_3$]<2.86 ($COCH_3$).[32]

Under the same reaction conditions except for the reaction times as in **1b**→**2b**, 3-formyl-**1e** and 3-hydroxymethyl-chlorins **1f** were iodinated to **2e** (78%) and **2f** (91%), respectively. The 3-formyl group slightly suppressed the yield of **1e** to **2e**, which was consistent with the result for the reaction of **1d** to **2d**. As expected, the reaction times enhanced with an increase of the electronegativity of the 3-substituents: 30 min/2.48 (**1b**, $3\text{-}CH_2CH_3$)<1 h/2.59 (**1f**, $3\text{-}CH_2OH$)<3 h/2.86 (**1e**, 3-CHO). The groups at the 3-position of methyl pyropheophorbides **1b**–**f** slightly affected the present iodination but the corresponding 20-iodochlorins **2b**–**f** were obtained in good yields without alteration of the 3-substituents.

2.2. Reaction of methyl 20-iodopyropheophorbides

Palladium-catalyzed cross-coupling of 20-iodochlorin **2b** with a tin reagent was first examined to confirm the reactivity of the 20-