Journal of Photochemistry and Photobiology A: Chemistry 313 (2015) 27–35

Contents lists available at ScienceDirect

Journal of Photochemistry and Photobiology A: Chemistry

journal homepage: www.elsevier.com/locate/jphotochem

Synthesis and self-aggregation of chlorophyll derivatives possessing a pyrazole ring at the C3 position

Yusuke Kinoshita, Hitoshi Tamiaki *

Graduate School of Life Sciences, Ritsumeikan University, Shiga, Kusatsu 525 8577, Japan

ARTICLE INFO

Article history:
Received 10 March 2015
Received in revised form 23 April 2015
Accepted 24 April 2015
Available online 11 May 2015

Keywords:
Diketonate
Fluorescence emission
Hydrazine
Methyl pyropheophorbide
UV–vis absorption

ABSTRACT

Chlorophyll compounds possessing an *N*-(un)substituted pyrazole ring at the C3 position were synthesized by the reaction of chlorophyll-*a* derivative having a trifluoromethyl-β-diketonate group with (substituted) hydrazines in 2,2,2-trifluoroethanol through the pyrazoline ring. The substituents on the C3-heterocyclic 5-membered ring affected the electronic absorption and emission of the monomeric chlorin molecules. Vis, CD and ^{1}H NMR spectra of the zinc chlorin bearing an *N*-unsubstituted pyrazole showed its dimerization in a nonpolar organic solvent.

1. Introduction

A main light-harvesting antenna system in green photosynthetic bacteria is called a chlorosome. The chlorosome is filled with numerous pigment molecules, bacteriochlorophylls(BChls)-*c*/*d*/*e*/*f* (see left in Fig. 1) [1–5]. Such BChls are constructed by a cyclic tetrapyrrole which is called a chlorin ring and some substituents are modified at the peripheral position of the chlorin π-skeleton. Magnesium (Mg) ion is coordinated at the central position of the chlorin chromophore. These BChls self-aggregate in a chlorosome to form well-ordered and large oligomers. Their self-aggregation is caused by the intermolecular interaction among the 3^1-hydroxy, central Mg ion and 13-carbonyl moieties, together with π–π interaction of chlorin macrocycles. In a chlorosome, a specific hydrogen bonding of the 3^1-hydroxy group coordinating the central Mg with the 13-carbonyl group is essential for the self-aggregation of the composite BChls. The intense interaction of Mg···O—H···O=C (coordination and hydrogen bonding) leads to their J-type self-aggregates with a slipped π–π fashion. The J-aggregates are oriented along the y-axis (N21–N23 line) of chlorin π-systems, so the red-most electronic (Qy) absorption bands move to a longer wavelength than that of the monomeric states.

For the purpose of understanding and applying the above natural photosynthetic systems, many model compounds have been designed and synthesized and their supramolecular self-aggregates in both a solution and a solid state have been reported [6]. As the typical models, chlorophyll (Chl) derivatives possessing a hydroxy group at the C3^1 position and a coordinated zinc ion at the central position self-aggregated to form similar oligomers as in natural chlorosomes [7–10]. Instead of the 3^1-hydroxy group, Chl derivatives possessing the 3^1-methoxy group were synthesized and formed J-aggregates under specific conditions [10–12]. Some zinc 3^1-amino-13^1-oxo-chlorins also formed their small and/or large aggregates in a nonpolar organic solvent [13–15]. The nitrogen atom at the C3^1 position intermolecularly coordinated to the central zinc ion to form large oligomers.

Some Chl derivatives possessing an azaaromatic group at the C3 position were prepared. Chl derivatives possessing a(n) (oligo) pyridyl group in the C3 substituent were synthesized by copper-free Sonogashira coupling of 3-ethynyl-chlorin with halogenated (oligo)pyridine [16,17]. Shinozaki et al. reported that the coordination of nitrogen atoms of pyridine and oxazole moieties to the zinc ion at the central position assisted self-aggregation of synthetic zinc Chl derivatives in a solution and crystals [18–20]. Chl derivatives directly connected with a triazole or a pyrazole group at the C3 position were synthesized from the corresponding C3-ethynylated chlorin with azides or diazomethane, respectively [21,22]. The *N*-unsubstituted pyrazole and triazole–chlorin conjugates self-aggregated in a nonpolar organic solvent.

A number of pyrazolylated compounds have been previously synthesized from the reaction of a β-dicarbonyl group with hydrazines for the construction of bioactive compounds and functional materials based on their strong coordination abilities [23–30]. Substituents of the β-dicarbonyl group and hydrazines as

---

* Corresponding author. Fax: +81 77 561 2890.
E-mail address: tamiaki@fc.ritsumei.ac.jp (H. Tamiaki).

http://dx.doi.org/10.1016/j.jphotochem.2015.04.018
1010-6030/© 2015 Elsevier B.V. All rights reserved.

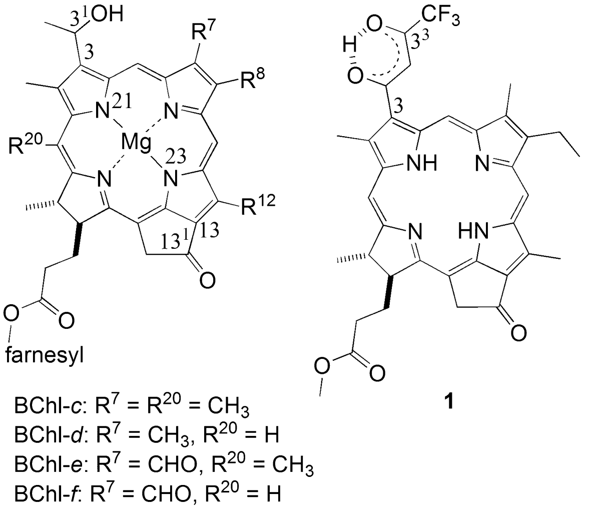

Fig. 1. Chemical structures of BChls in chlorosomes (left) and Chl derivative **1** possessing a trifluoromethyl-β-diketonate moiety at the C3 position (right).

well as the reaction solvents affected their cycloadditions including the regioselectivity and successive dehydration. We have recently reported preparation of Chl derivative **1** possessing a trifluoromethyl-β-diketonate group at the C3 position by the Claisen condensation of methyl 3-acetyl-pyropheophorbide-*a* with ethyl trifluoroacetate in the present of sodium methoxide (right in Fig. 1) [31,32]. The trifluoromethyl-β-diketonate group of **1** was regioselectively reacted with butyl amines at room temperature to afford the hemiaminal: –C3^3(OH)(NHBu)CF$_3$ [33]. In this work we reported the synthesis and optical properties of Chl derivatives possessing a substituted pyrazole ring at the C3 position from the reaction of **1** with (un)substituted hydrazines. The synthetic Chl derivative directly connected with an *N*-unsubstituted pyrazole dimerized with a head-to-tail fashion in a nonpolar organic solvent.

2. Experimental

2.1. General

^{1}H NMR spectra were measured by a JEOL JNM-ECA-600 spectrometer at 600 MHz. Chemical shifts are reported relative to the residual undeuterated solvent peak: δ_H = 7.26 ppm (CHCl$_3$). COSY and NOESY techniques were used to assign the NMR peaks. Time-of-flight mass data were obtained using direct laser desorption/ ionization (LDI) by a Shimadzu AXIMA-CFR plus spectrometer. High resolution mass spectra (HRMS) were recorded on a Bruker micrOTOF II spectrometer: atmospheric pressure chemical ionization (APCI) and positive mode in an acetonitrile solution. Thin layer chromatography (TLC) and flash column chromatography (FCC) were performed with silica gel (Merck, Kieselgel 60 F_{254} and 230–400 mesh). Electronic absorption and circular dichroism (CD) spectra were obtained on a Hitachi U-3500 spectrophotometer and a Jasco J-720W spectrophotometer, respectively. Fluorescence emission spectra and quantum yields were obtained by a Hamamatsu Photonics C9920-03G spectrometer. Hydrazine monohydrate (reagent grade, 98%) was purchased from Sigma–Aldrich. Methylhydrazine, phenylhydrazine and *p*-toluenesulfonic acid monohydrate were purchased from Wako Pure Chemical Industries. 2,2,2-Trifluoroethanol (TFE) was purchased from Tokyo Chemical Industry. Toluene was purchased from Nacalai Tesque. Dichloromethane and hexane for measurements of optical spectra were purchased from Nacalai Tesque as prepared specially for spectroscopy and used as supplied.

Methyl 3-devinyl-3-(4′,4′,4″-trifluoro-1′,3″-dioxo-butan-1″-yl)-pyropheophorbide-*a* enol (**1**) was prepared according to reported procedures [31].

2.2. Synthesis of methyl 3-devinyl-3-(5′-hydroxy-5′-trifluoromethyl-2′-pyrazolin-3′-yl)pyropheophorbide-a (2)

To a TFE solution (4 mL) of diketonated chlorin **1** (29.4 mg, 44.5 μmol) was added hydrazine monohydrate (50 μL, 1.0 mmol) and the mixture was stirred at room temperature under nitrogen in the dark. After the starting chlorin disappeared (checked by TLC), the reaction mixture was diluted with dichloromethane, washed with water several times and dried over sodium sulfate. All the solvents were evaporated and the residue was purified with FCC (Et$_2$O:CH$_2$Cl$_2$ = 10:90) and recrystallization (CH$_2$Cl$_2$ and hexane) to give 2-pyrazoline–chlorin conjugate **2** (8.8 mg, 13.0 μmol, 29%) as a 1:1 mixture of the 3^1-epimers: black solid; VIS (CH$_2$Cl$_2$) λ_{max} 675 (relative intensity, 44%), 618 (8), 543 (9), 511 (11), 413 (100) 383 (shoulder, 63), 325 nm (24); ^{1}H NMR (600 MHz, CDCl$_3$) δ (3^3*R*:3^3*S* = 1:1) 9.91/9.76 (1H, s, 5-H), 8.81/8.71, (1H, s, 10-H), 8.35/8.15 (1H, s, 20-H), 6.92/6.91 (1H, s, 3^3-NH), 5.08/4.88, 4.95/4.76 (each 1H, d, *J* = 19 Hz, 13-CH$_2$), 4.25, 4.08 (each 1H, d, *J* = 18 Hz, 3^1-CH$_2$), 4.25/4.14 (1H, m, 18-H), 3.83/3.73 (1H, m, 17-H), 3.82/3.65 (3H, s, 17^2-COOCH$_3$), 3.47/3.44 (3H, s, 2-CH$_3$), 3.43/3.41 (3H, s, 12-CH$_3$), 3.40/3.28 (2H, m, 8-CH$_2$), 3.12/3.00 (3H, s, 7-CH$_3$), 2.69 – 2.62, 2.59 – 2.53, 2.53 – 2.45, 2.35 – 2.24, 2.17 – 2.08, 2.07 – 1.96 (4H, m, 17-CH$_2$CH$_2$), 1.70/1.44 (3H, t, *J* = 7 Hz, 18-CH$_3$), 1.44 (3H, m, 8^1-CH$_3$), –0.5/–1.0 (1H, br, NH), –2.45/–2.85 (1H, s, NH) [The 5′-OH signal was invisible.]; MS (LDI) found *m*/*z* = 674, calcd. for C$_{36}$H$_{37}$N$_6$O$_4$F$_3$: M$^+$, 674; HRMS (APCI) found: *m*/*z* = 675.2902, calcd. for C$_{36}$H$_{38}$N$_6$O$_4$F$_3$: MH$^+$, 675.2901.

2.3. Synthesis of methyl 3-devinyl-3-(5′-trifluoromethyl-pyrazol-3′-yl)-pyropheophorbide-a (3)

To a toluene solution (4 mL) of 5-hydroxy-2-pyrazoline analog **2** (9.3 mg, 13.8 μmol) was added *p*-toluenesulfonic acid monohydrate (23.4 mg, 59.4 μmol) and the mixture was stirred at room temperature under nitrogen in the dark. After the started chlorin disappeared (checked by TLC), the reaction mixture was extracted with dichloromethane and the combined organic phase was washed with water, aqueous 4% sodium hydrogen carbonate, and dried over sodium sulfate. All the solvents were evaporated and the residue was purified with FCC (Et$_2$O:CH$_2$Cl$_2$ = 10:90) and recrystallization (CH$_2$Cl$_2$ and hexane) to give pyrazole–chlorin conjugate **3** (2.9 mg, 4.4 μmol, 32%): dark brown solid; VIS (CH$_2$Cl$_2$) λ_{max} 671 (relative intensity, 58%), 614 (7), 538 (9), 508 (10), 411 (100), 381 (shoulder, 62), 320 nm (20); ^{1}H NMR (CDCl$_3$) δ 9.09, 9.00, 8.56 (each 1H, s, 5, 10, 20-H), 7.22 (1H, s, 3^2-H), 4.74, 4.67 (each 1H, d, *J* = 19 Hz, 13^1-CH$_2$), 4.37 (1H, dq, *J* = 3, 8 Hz, 18-H), 3.98 (1H, dt, *J* = 10, 3 Hz, 17-H), 3.70, 3.39, 3.22, 3.13, (each 3H, s, 2, 7, 12-CH$_3$, 17^2-COOCH$_3$), 3.59 (2H, q, *J* = 8 Hz, 8-CH$_2$), 2.59 – 2.52, 2.46 – 2.41, 2.38 – 2.26 (1H + 1H + 2H, m, 17-CH$_2$CH$_2$), 1.68 (3H, d, *J* = 8 Hz, 18-CH$_3$), 1.61 (3H, t, *J* = 8 Hz, 8^1-CH$_3$), –0.98, –2.48 (each 1H, NH × 2) [The NH signal of pyrazole moiety was invisible.]; MS (LDI) found *m*/*z* = 656, calcd. for C$_{36}$H$_{35}$N$_6$O$_3$F$_3$: M$^+$, 656; HRMS (APCI) found: *m*/*z* = 657.2798, calcd. for C$_{36}$H$_{36}$N$_6$O$_3$F$_3$: MH$^+$, 657.2796.

2.4. Synthesis of zinc methyl 3-devinyl-3-(5′-trifluoromethyl-pyrazol-3′-yl)-pyropheophorbide-a (Zn-3)

To a dichloromethane solution (10 mL) of free base **3** (3.2 mg, 4.9 μmol) was added a methanol solution (3 mL) saturated with zinc acetate dihydrate and the mixture was stirred at room temperature for three hours under nitrogen in the dark. The reaction mixture was washed with aqueous 4% sodium hydrogen