doi:10.1246/cl.2012.820

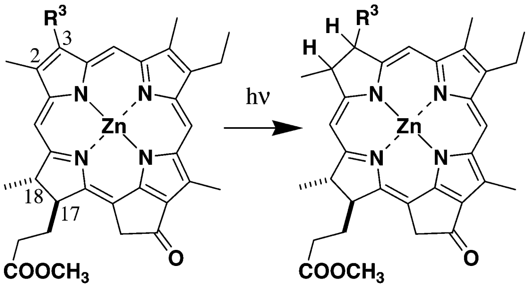
Photoreduced Deformylation of Zinc Chlorophyll-*d* Derivative

Hitoshi Tamiaki,* Meiyun Xu, and Shinnosuke Machida
Graduate School of Life Sciences, Ritsumeikan University, Kusatsu, Shiga 525-8577

(Received May 18, 2012; CL-120434; E-mail: tamiaki@fc.ritsumei.ac.jp)

Photochemical reaction of a zinc chlorophyll-*d* derivative possessing a formyl group at the 3-position with a reductant in a deaerated alcoholic solution gave the corresponding 3-unsubstituted chlorin in 43% yield based on consumed starting material. The novel deformylation was accompanied by expected 2,3- or 7,8-dihydrogenation to give minor products possessing a isobacteriochlorin or bacteriochlorin π-system, respectively, as stereochemical mixtures.

Photoreduction of zinc methyl pyropheophorbide-*a*, the zinc complex of a 3-vinyl-17,18-dihydroporphyrin, prepared by modifying chlorophyll-*a* was reported earlier to afford 2,3-*cis*-dihydrogenated compounds bearing an isobacteriochlorin (2,3,17,18-tetrahydroporphyrin) π-system in ca. 55% yield (Scheme 1).[1] Similar photoreduction of zinc 3-acetylchlorin, another chlorophyll-*a* derivative, was recently reported to give the corresponding 2,3-*trans*-isobacteriochlorins as chemically stable products in 94% conversion yield.[2] In a series of the photoreductions, zinc methyl pyropheophorbide-*d* (**1**) possessing the 3-formyl group was examined and its 3-deformylation was first observed as well as its hydrogenation expected from the above reports (Scheme 2).

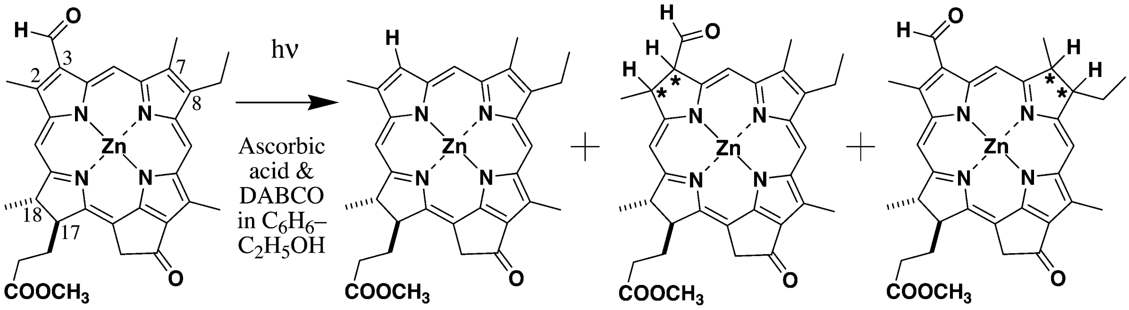


Zinc 3-substituted chlorin Zinc isobacteriochlorins
R^3 = CH=CH$_2$, COCH$_3$

Scheme 1. Photoreduction (2,3-dihydrogenation) of zinc methyl pyropheophorbides to the corresponding isobacteriochlorins.

When zinc 3-formylchlorin **1** in 10% (v/v) ethanol and benzene saturated with nitrogen gas was irradiated with visible light in the presence of ascorbic acid and 1,4-diazabicyclo[2.2.2]octane (DABCO) at room temperature, three types of products were found by HPLC analysis (Figure S1 in Supporting Information[9]). At the retention time of 4 to 6 min, four new peaks were observed after photoreaction. All the bands had the same visible absorption maxima ($\lambda_{\max}$) at 598, 418, and 400–390 nm (Figures S1G–S1J[9]). These spectra show that they are 2,3-dihydrogenated products **3** possessing an isobacteriochlorin π-system, compared with reported data of related compounds.[1,2] They gave the same mass peak at m/z 615 (LC-MS by atmospheric pressure chemical ionization) which was two units larger in mass number than that of protonated **1** (m/z 613 [MH$^+$]), also supporting that they are dihydrogenated compounds of **1**. The four products are assigned to be stereoisomers of zinc isobacteriochlorins **3**: two 2,3-*cis*-forms with (2*R*,3*S*)- and (2*S*,3*R*)-configurations as well two 2,3-*trans*-forms with (2*R*,3*R*)- and (2*S*,3*S*)-configurations. The 2,3-hydrogenation was expected from previous reports.[1,2] The two *cis*-adducts were initially produced and the epimerization at the C3-position then occurred through enolization (C3=CHOH) to give the two *trans*-forms. It is noted that stereoselective hydrogenation was hardly observed in the present system bearing a less sterically demanding formyl group at the 3-position, while thermodynamically more stable *trans*-isobacteriochlorins were predominantly formed in photoreduction of zinc 3-acetylchlorin.[2]

In the HPLC of the photoreaction mixture, three new peaks were additionally observed between 9 and 12 min (Figure S1D). All of them gave near-infrared/visible absorption bands at $\lambda_{\max}$ = ca. 790/590 nm and a mass peak at m/z 615. The observed maxima are typical of Q_y/Q_x absorption in bacterio-



Zinc 3-formylchlorin **1** Zinc 3-unsubstituted chlorin **2** Isobacteriochlorins **3** Bacteriochlorins **4**

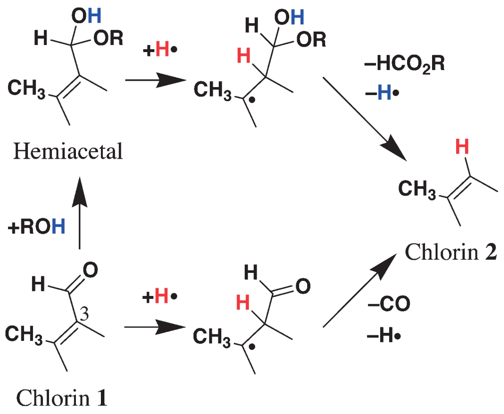
Scheme 2. Photoreduction of zinc methyl pyropheophorbide-*d* (**1**) to zinc methyl 3-deformylpyropheophorbide-*d* (**2**), zinc isobacteriochlorins **3**, and zinc bacteriochlorins.

chlorin (7,8,17,18-tetrahydroporphyrin) π-systems[3] and the MS data confirm them to be isomers of **3**. As a result, they are assigned to be zinc bacteriochlorins **4** as 7,8-dihydrogenated products. The three obtained bands would contain four stereoisomers of *cis*- and *trans*-adducts **4** as in **3** (vide supra) and two of them seem to be overlapped under the present HPLC conditions.

One more peak appeared at the HPLC retention time of 16 min and was the major product after irradiation for 1 min (Figure S2).[4] After purification by HPLC, the 1D and 2D ^{1}H NMR spectra of the isolated product in $CDCl_3$ gave no singlet peak of a formyl group at around 11 ppm but a new quartet peak of one proton at 8.57 ppm coupled with the 2-CH_3, which was assigned to the 3-H (Figures S3 and S4).[5] The visible spectrum ($\lambda_{max} = 645$ and 421 nm in CH_2Cl_2) is similar to those of zinc chlorophyll derivatives possessing a chlorin π-system.[6] The mass data (m/z 585 [MH^+]) show that a carbonyl group (28 in mass number) was lost by its formation. Therefore, the major product was assigned to be zinc 3-unsubstituted chlorin **2**. The authentic sample was prepared by zinc metallation of methyl 3-deformylpyropheophorbide-*d* (see Experimental section in Supporting Information[9]) which recently became available from pyrolysis of the corresponding 3-carboxychlorin.[6] All the data of the isolated product were identical to those of the authentic sample **2**. After 1 min illumination, 67% of **1** was recovered and **2** was obtained in 14% yield, so the conversion yield of **2** based on consumed **1** is estimated to be 43%: small amounts of **3** and **4** were detected by HPLC. Since **2** was photolabile, it decreased in amount during prolonged illumination, especially after disappearance of half the amount of starting **1**.

The present deformylation of **1** to **2** could not be observed, if any one of the following four factors was absent in the reaction: illumination with visible light, ascorbic acid, DABCO, or ethanol. The deformylation mechanism under the photoreduced conditions is unclear at present but speculated to be as follows. Since no deacetylation could be detected in the photoreduction of the corresponding zinc 3-acetylchlorin, the sterically less hindered C3-position of zinc 3-formylchlorin **1** or its derivative might be attacked by some hydrogen species. The photodeformylation occurred even in the presence of methanol instead of ethanol and alcohol is necessary as a cosolvent. The 3-formyl group would be partially transformed to a hemiacetal with ethanol or ascorbic acid (Scheme 3). The resulting hemiacetal (or the original aldehyde) was photoexcited and attacked at the C3-position by hydrogen species including a hydrogen radical. Successive removal of any formate (or carbon monoxide), regeneration of hydrogen species and aromatization to reform the chlorin π-system gave ultimately **2**.

Removal of a formyl group directly conjugated with porphyrinoids in melted resorcinol at 180–200 °C was reported earlier,[7] but no photoinduced deformylation in any porphyrinoids had been reported in the literature, to our best knowledge. The first observation of deformylation in zinc 3-formylchlorin **1** to **2** under mild illuminated conditions might lead to facile access to any other β-unsubstituted chlorophylls. In the degradation of naturally occurring chlorophylls-*d*/*f* (magnesium 3/2-formylchlorins),[8] their deformylation can occur under anoxygenic (reduced) conditions in a photic zone. Photochemical reduction of metalloporphyrinoids possessing a formyl group at any peripheral position is underway.



Scheme 3. Proposed reaction pathways of zinc 3-formylchlorin **1** to zinc 3-unsubstituted chlorin **2** (in the case of attack by a hydrogen radical).

We thank Dr. Taichi Yoshitomi of Ritsumeikan University for measurements of LC-MS. This work was partially supported by a Grant-in-Aid for Scientific Research (A) (No. 22245030) from the Japan Society for the Promotion of Science (JSPS).

References and Notes

1 D. J. Simpson, K. M. Smith, *J. Am. Chem. Soc.* **1988**, *110*, 2854.
2 H. Tamiaki, M. Xu, T. Mizoguchi, *Tetrahedron Lett.* **2012**, *53*, 3210.
3 S.-i. Sasaki, H. Tamiaki, *J. Org. Chem.* **2006**, *71*, 2648.
4 Zinc 3-formylchlorin **1** (1.3 mg, 2.1 µmol) was dissolved in 10% (v/v) EtOH/C_6H_6 (38 mL) and bubbled with N_2 for 20 min. Ascorbic acid (30.4 mg, 173 µmol) and DABCO (53.2 mg, 474 µmol) were added to the solution and bubbled with N_2 for 5 min. The solution in a sealed vessel was irradiated with a 250 W halogen lamp (ELMO slide projector OMNI 253 AF, 350–700 nm). Photoreaction was monitored by visible absorption spectroscopy: an appearance of the peak at about 650 nm and a concomitant disappearance of the peak at about 690 nm. After irradiation for 1 min, the reaction mixture was evaporated in vacuo, then flashed with nitrogen gas to remove all the solvents. The residue was purified by HPLC (Cosmosil 5C_{18}-AR-II, 4.6ϕ × 150 mm, 15% H_2O/MeOH, 2.0 mL min^{-1}): retention times of **1** and zinc 3-unsubstituted chlorin **2** were 12 and 16 min, respectively. The separated HPLC fractions were poured into water and extracted with CH_2Cl_2. The organic layer was evaporated in vacuo to give pure samples.
5 Zinc 3-unsubstituted chlorin **2**: dark green solid; mp 137–142 °C; Vis (CH_2Cl_2): λ_{max} 645 (relative absorbance, 0.72), 600 (0.12), 554 (0.07), 514 (0.05), 421 (1.00), 401 (0.69), 312 nm (0.24); ^{1}H NMR ($CDCl_3$): δ 9.32 (1H, s, 10-H), 8.95 (1H, s, 5-H), 8.57 (1H, br-q, $J = 1$ Hz, 3-H), 8.40 (1H, s, 20-H), 4.94, 4.85 (each 1H, d, $J = 19$ Hz, 13^1-CH_2), 4.43 (1H, dq, $J = 2$, 8 Hz, 18-H), 4.21 (1H, dt, $J = 8$, 2 Hz, 17-H), 3.59$_2$, 3.59$_0$ (each 1H, q, $J = 8$ Hz, 8-CH_2), 3.50 (3H, s, 12-CH_3), 3.41 (3H, s, 17^2-$COOCH_3$), 3.34 (3H, d, $J = 1$ Hz, 2-CH_3), 3.12 (3H, s, 7-CH_3), 2.57–2.52, 2.33–2.26 (each 1H, m, 17-CH_2), 2.48–2.43, 2.22–2.16 (each 1H, m, 17^1-CH_2), 1.83 (3H, d, $J = 8$ Hz, 18-CH_3), 1.63 (3H, t, $J = 8$ Hz, 8^1-CH_3); MS (TOF) m/z 585.7, MH^+ calcd for $C_{32}H_{33}N_4O_3Zn$, 585.2.
6 H. Tamiaki, S. Machida, K. Mizutani, *J. Org. Chem.* **2012**, *77*, 4751.
7 H. Fischer, A. Wunderer, *Justus Liebigs Ann. Chem.* **1938**, *533*, 230; P. S. Clezy, J. Barrett, *Biochem. J.* **1961**, *78*, 798.
8 H. Miyashita, H. Ikemoto, N. Kurano, K. Adachi, M. Chihara, S. Miyachi, *Nature* **1996**, *383*, 402; M. Chen, M. Schliep, R. D. Willows, Z.-L. Cai, B. A. Neilan, H. Scheer, *Science* **2010**, *329*, 1318.
9 Supporting Information is also available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.