Pergamon

Tetrahedron Letters, Vol. 38, No. 2, pp. 267-270, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(96)02278-2

Self-Aggregation of Synthetic Zinc Chlorins Possessing "Inverse" Keto and Hydroxyl Groups

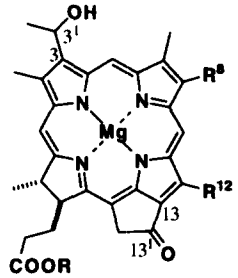
Hitoshi Tamiaki,* Tomohiro Miyatake and Rikuhei Tanikaga

Department of Bioscience and Biotechnology, Faculty of Science and Engineering, Ritsumeikan University, Kusatsu, Shiga 525-77, Japan

Abstract: Zinc 3-acetyl-13^1-hydroxychlorin Zn-**4** was efficiently prepared as a model for naturally occurring bacteriochlorophyll-*d* possessing 3^1-hydroxyl and 13-keto groups. Synthetic model Zn-**4** self-aggregates to form oligomers in non-polar organic solvents as well as the isomeric zinc 3^1-hydroxy-13^1-oxochlorin Zn-**1**. Both the *in-vitro* aggregates are similar with the *in-vivo* aggregates of bacteriochlorophyll-*d* in the main light-harvesting antennae of photosynthetic green bacteria.

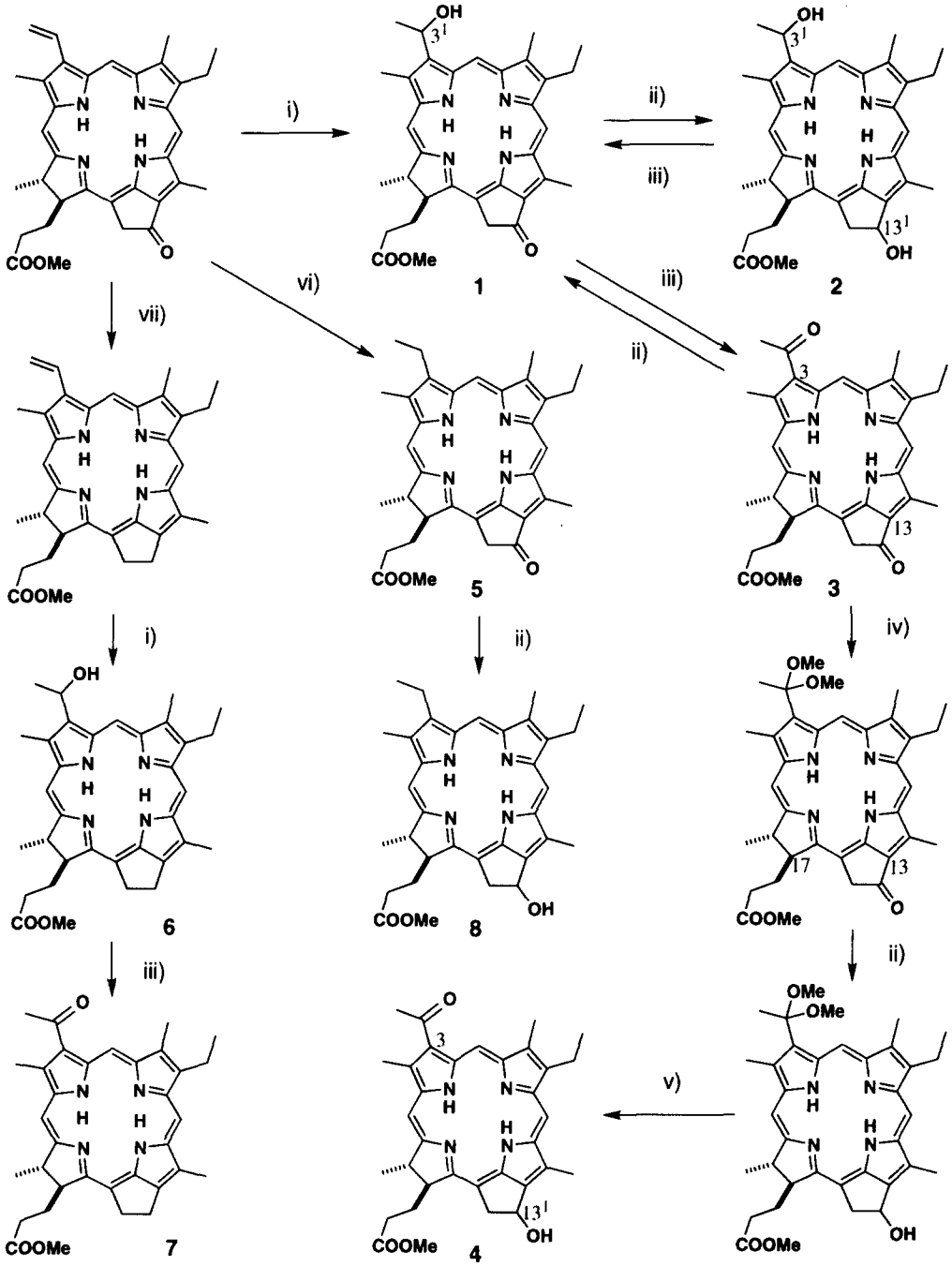
Bacteriochlorophyll(=BChl)s-*c* and *d* self-aggregate *in-vivo* to form the main light-harvesting antennae (=chlorosomes) of photosynthetic green bacteria.[1] Such supramolecules are unique compared to the normal antenna complexes which are built up by interaction of pigments with peptides.[2] Supramolecular structures of *in-vivo* chlorosomes have been extensively investigated, which clarified that *in-vitro* self-aggregates of BChls-*c*/*d* and the zinc analogues in non-polar organic solvents are good models for the natural chlorosomal aggregates.[1,3,4] The model experiments showed that central magnesium (or zinc), 3^1-hydroxyl and 13-keto carbonyl groups are necessary for the self-aggregation.[3h] Here we report on the synthesis of novel zinc chlorins Zn-**4** possessing 13^1-hydroxyl and 3-keto carbonyl groups in the molecule and the aggregation of the synthetic Zn-**4** in non-polar organic solvents.

One representative of BChl-*d* molecules (see Fig. 1) has R^8=Et, R^{12}=Me and R=farnesyl and the absolute configuration at the 3^1-position is (*R*).[5] We have already reported that (3^1-*R*)-isomer of methyl zinc bacteriopheophorbide-*d* (Zn-**1**; Mg→Zn, R^8=Et, R^{12}=R=Me in Fig. 1) self-aggregates to form oligomers in non-polar organic solvents.[6] We tried to prepare zinc chlorins Zn-**4** (see Scheme 1) possessing 13^1-hydroxyl and 3-keto carbonyl groups where both the groups are situated at the symmetrical positions compared with normal BChl-*d*. First, selective oxidation of 3^1,13^1-diol **2** (see Scheme 1) was checked for preparation of desired 13^1-hydroxy-3-acetyl-chlorin **4**. Most oxidants including $KMnO_4$[7] gave mainly decomposition products, but oxidation by $Pr_4N(RuO_4)$–*N*-methylmorpholine *N*-oxide[8] was useful for transformation of hydroxyl to keto group without undesired decomposition. During the mild oxidation, the 13^1-hydroxyl group was oxidized to keto group more rapidly than 3^1-OH and gave a mixture of 4 compounds **1**–**4** which were separated to afford the major 13-ketone **1** and a small



3^1-configuration=*R*, *S*
R^8=Et, ^{n}Pr, ^{i}Bu, ^{neo}Pn
R^{12}=Me, Et
R=a long chain

Fig. 1. Bacteriochlorophyll(=BChl)-*d*



Scheme 1. Reagents and conditions: (reactions at room temparature unless otherwise noted): i) HBr / AcOH (55 °C), CH_2N_2 / Et_2O; ii) $NaBH_4$ / MeOH–CH_2Cl_2; iii) Pr_4NRuO_4–$Me(O)N(CH_2CH_2)_2O$ / CH_2Cl_2; iv) $CH(OCH_3)_3$ / CH_2Cl_2, HCl / MeOH; v) 5% aq. HCl; vi) H_2 / Pd–C / CH_3COCH_3; vii) $NaBH_4$–TFA / CH_2Cl_2.

amount of 3-acetyl derivative **4** as mono-keto products (**1** : **4** ≈ 3 : 1). Then, selective reduction of 3,13-diketone **3** was checked by several boron reagents including $NaBH_4$ and rapid reduction of the 3-keto group afforded predominantly 3^1-hydroxyl compound **1** with a trace of the 13^1-hydroxyl isomer **4**. These results indicate that the 3^1-position is more reactive than 13^1-position probably because the 13-keto group is more conjugated with the chlorin π-chromophore and more stable than the 3-keto group. Finally, protection of reactive 3-acetyl group[9] of **3** and successive reduction of the 13-keto group gave nearly quantitatively the desired 13^1-hydroxy-3-acetylchlorin **4** after removal of the protection group as shown in Scheme 1. Zinc metallation of **4** was carried out by the reported procedures[10] and the diastereomeric isomers (13^1-*R*/*S*)-Zn-**4** produced were easily separated by a single HPLC run.[11] The 13^1-configuration was determined by ^1H NMR techniques (COSY and NOESY). The ratio of (13^1-*R*)- and (13^1-*S*)-isomers was 1.4 : 1, indicating that the 13-keto group was reduced slightly stereoselectively (17% d.e.) mainly due to the steric effect of the propionate substituent on the neighboring 17-position. Other chlorin compounds **5**–**8** without hydroxyl or keto groups were also synthesized (see Scheme 1).

All model compounds were monomeric in a diluted dichloromethane solution (ca. 10^{-5} mol dm^{-3}) and the solutions showed sharp bands in the visible absorption spectra. In non-polar organic solvents (e.g., hexane or cyclohexane with a small amount of dichloromethane or tetrahydrofuran), zinc 3^1-hydroxy-13-oxochlorins including Zn-**1** were oligomeric and the visible bands were red-shifted and broadened.[1a,3b,e,h,6] Especially, the red shift of the Q_y peak clearly shows aggregation of these type compounds.[3h] Table 1 summarized the wavelengths of Q_y peaks of synthetic chlorins in solutions, indicating that (13^1-*S*)-Zn-**4** self-aggregated to form oligomers as well as (3^1-*R*)-Zn-**1**.[12] Compounds which lack one of central zinc (as in **1** and **4**), hydroxyl (as in Zn-**5** and Zn-**7**) and keto groups (as in Zn-**6** and Zn-**8**) hardly aggregated to be almost monomeric species in non-polar solvents. Therefore, zinc chlorins (as in Zn-**1** and Zn-**4**) possessing hydroxyl and keto groups on the Q_y axis (N21–N23 axis) self-aggregate to form oligomers as does BChl-*d*, and the positions of the two groups are not important for self-aggregation.[13]

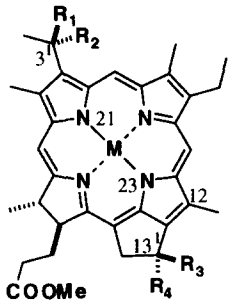


Table 1. Q_y maxima of model compounds and BChl-*d* (ca. 10^{-5} mol dm^{-3})

	M	R_1	R_2	R_3	R_4	λ_{max} / nm	
						CH_2Cl_2	1%(v/v)CH_2Cl_2 –hexane
(3^1-*R*)-Zn-**1**	Zn	OH	H	=O		648	705
(3^1-*R*)-**1**	H_2	OH	H	=O		659	659
Zn-**5**	Zn	H	H	=O		644	640
(3^1-*R*)-Zn-**6**	Zn	OH	H	H	H	615	615[a]
(13^1-*S*)-Zn-**4**	Zn	=O		OH	H	644	709
(13^1-*S*)-**4**	H_2	=O		OH	H	664	664
Zn-**7**	Zn	=O		H	H	638	636
(13^1-*S*)-Zn-**8**	Zn	H	H	OH	H	618	618
BChl-*d*[b]	Mg	OH	H	=O		658	714[c]

[a] A small shoulder appeared on the red side of Q_y band around 630 nm. [b] Me/Et =20/1 at the 12-position and farnesyl ester. [c] In natural chlorosomes, see ref. 5.

ACKNOWLEDGMENTS

We thank Dr. Shin'ichi Kondo and Mr. Shoichiro Takeuchi for their experimental assistance and also Prof. Dr. Kurt Schaffner and Prof. Dr. Alfred R. Holzwarth for their helpful discussion. This work was partially supported by Kato Memorial Bioscience Foundation, Ritsumeikan Academic Research Grant for Overseas Joint Studies.

REFERENCES AND NOTES

1. Recent reviews: (a) Tamiaki, H. *Coord. Chem. Rev.* **1996**, 148, 183–197. (b) Blankenship, R. E.; Olson, J. M.; Miller, M. In *Anoxygenic Photosynthetic Bacteria*; Blankenship, R. E.; Madigan, M. T.; Bauer, C. E. Eds.; Kluwer: Netherlands, 1995; pp. 399–435.
2. Two crystal structures of intramembraneous antennae of photosynthetic bacteria were recently reported; McDermott, G.; Prince, S. M.; Freer, A. A.; H.-Lawless, A. M.; Papiz, M. Z.; Cogdell, R. J.; Isaacs, N. W. *Nature* **1995**, 374, 517–521; Koepke, J.; Hu, X.; Muenke, C.; Schulten, K.; Michel, H. *Structure* **1996**, 4, 581–597.
3. Structural models: (a) Bystrova, M. I.; Mal'gosheva, I. N.; Krasnovskii, A. A. *Mol. Biol.* **1979**, 13, 440–451. (b) Smith, K. M.; Kehres, L. A.; Fajer, J. *J. Am. Chem. Soc.* **1983**, 105, 1387–1389. (c) Brune, D. C.; Nozawa, T.; Blankenship, R. E. *Biochemistry* **1987**, 26, 8644–8652. (d) Nozawa, T.; Ohtomo, K.; Suzuki, M.; Morishita, M.; Madigan, M. T. *Bull. Chem. Soc. Jpn.* **1993**, 66, 231–237. (e) Cheng, P.; Liddell, P. A.; Ma, S. X. C.; Blankenship, R. E. *Photochem. Photobiol.*, **1993**, 58, 290–295. (f) Chiefari, J.; Griebenow, K.; Fages, F.; Griebenow, N.; Balaban, T. S.; Holzwarth, A. R.; Schaffner, K. *J. Phys. Chem.* **1995**, 99, 1357–1365. (g) Dudkiwiak, A.; Francke, C.; Amesz, J. *Photosynth. Res.* **1995**, 46, 427–433. (h) Tamiaki, H.; Amakawa, M.; Shimono, Y.; Tanikaga, R.; Holzwarth, A. R.; Schaffner, K. *Photochem. Photobiol.* **1996**, 63, 92–99.
4. Functional models: Tamiaki, H.; Miyatake, T.; Tanikaga, R.; Holzwarth, A. R.; Schaffner, K. *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 772–774.
5. Smith, K. M.; Goff, D. A. *J. Chem. Soc., Perkin Trans. I* **1985**, 1009–1113.
6. Tamiaki, H.; Takeuchi, S.; Tanikaga, R.; Balaban, S. T.; Holzwarth, A. R.; Schaffner, K. *Chem. Lett.* **1994**, 401–402.
7. Seely, G. R. In *The Chlorophylls*; Vernon, L. P.; Seely, G. R. Eds.; Academic: London, 1969; pp. 67.
8. Shiau, F.-Y.; Pandey, R. K.; Ramaprasad, S.; Dougherty, T. J.; Smith, K. M. *J. Org. Chem.* **1990**, 55, 2190–2195.
9. Falk, H.; Hoonerart, G.; Iserning, H.-P.; Eschenmoser, A. *Helv. Chim. Acta* **1975**, 58, 2347–2357.
10. Tamiaki, H.; Miyata, S.; Kureishi, Y.; Tanikaga, R. *Tetrahedron* **1996**, 38, 12421–12432.
11. Under the conditions of Cosmosil $5C_{18}$-AR, 4.6x150 mm, Nacalai Tesque, $CH_3OH:H_2O$=8:1, 1.0 ml/min, (13^1-*S*)-Zn-**4** and (13^1-*R*)-Zn-**4** were readily separated (R_s = 3.0). The retention times were 3.5 and 4.2 min, respectively. All new compounds were characterized by ^{1}H-NMR, VIS, IR and/or MS spectra. Synthetic procedures will be reported elsewhere.
12. *In-vitro* aggregates of (3^1-*S*)-Zn-**1** and (13^1-*R*)-Zn-**4** had also red-shifted Q_y bands of λ_{max} = 648 → 697 and 644 → 673, 710 (sh) nm, respectively. Such diastereoselective controls were reported, see ref. 6 and 13.
13. Very recently, Jesorka *et al.* reported that zinc 3-formyl-13^1-hydroxychlorins self-aggregated *in-vitro*; Jesorka, A.; Balaban, T. S.; Holzwarth, A. R.; Schaffner, K. *Angew. Chem.* **1996**, in press.

(*Received in Japan* 28 *October* 1996; *accepted* 15 *November* 1996)