Available online at www.sciencedirect.com

SCIENCE DIRECT®

ELSEVIER

Tetrahedron Letters 47 (2006) 4849–4852

Tetrahedron
Letters

Trifluoroacetyl-chlorin as a new chemosensor for alcohol/amine detection

Shin-ichi Sasaki, Yuki Kotegawa and Hitoshi Tamiaki*

Department of Bioscience and Biotechnology, Faculty of Science and Engineering, Ritsumeikan University, Kusatsu, Shiga 525-8577, Japan

Received 12 April 2006; revised 1 May 2006; accepted 8 May 2006
Available online 30 May 2006

Abstract—Chlorophyll derivative possessing a trifluoroacetyl group at the 3-position was synthesized as a new chemosensor for alcohols and amines. Intense Q_y peak of the trifluoroacetyl-chlorin (701 nm in $CHCl_3$) showed blue shifts to 667 nm in MeOH and 665 nm in n-$BuNH_2$ due to the formation of the corresponding hemiacetal and hemiaminal with visible color changes. Thermodynamic parameters for the complexation between trifluoroacetyl-chlorin and n-$BuNH_2$ in $CDCl_3$ were determined to be $\Delta H = -48\ \text{kJ mol}^{-1}$ and $\Delta S = -147\ \text{J K}^{-1}\ \text{mol}^{-1}$. Ratiometric fluorescence sensing of n-$BuNH_2$ in THF was also demonstrated.

Development of chemically functional dyes is of current interest due to their possible application in the field of analytical chemistry, and many chromo/fluororeceptors for the selective recognition of biologically important species have been synthesized.[1] However, there is no report on chemosensors using a chlorophyll derivative as their main dye unit, to the best of our knowledge. Chlorophyll-*a* is a representative dye molecule in natural photosynthesis,[2] and has an intense Q_y peak at around 660 nm in its monomeric state. During our synthetic studies of chlorophyll-*a* derivatives,[3] we found that the modification of the substituents on a chlorin macrocycle strongly affected the position of the Q_y peak. For example, reduction of the C3-formyl to hydroxymethyl group of methyl pyropheophorbide-*d* caused a large blue-shift of the Q_y peak from 695 to 662 nm in CH_2Cl_2.[4] Therefore, introduction of a suitable functional group on the chlorin macrocycle is expected to lead to the development of new chemosensors, which enable guest sensing at a longer-wavelength region with less interference from environments and impurities. A trifluoroacetyl group is selected as an example of this purpose. Although trifluoroacetophenone derivatives have been exclusively used as ionophores for carbonate-selective electrodes,[5,6] recent reports include applications as sensing components toward alcohols,[7] amines,[8] anions,[9] or amino acids.[10] The functional group can reversibly form adducts with those analytes, and stylbene,[7a] azobenzene,[8] pyrene,[10b] and dansyl units[9b] have been used as chromo/fluorogenic dye moieties. In this letter, we report the synthesis of a chlorophyll derivative possessing the 3-trifluoroacetyl group. Its hemiacetal and hemiaminal formation in solution was investigated by NMR and vis spectroscopies and its fluorescent ratiometric sensing for n-$BuNH_2$ was demonstrated in THF.[11]

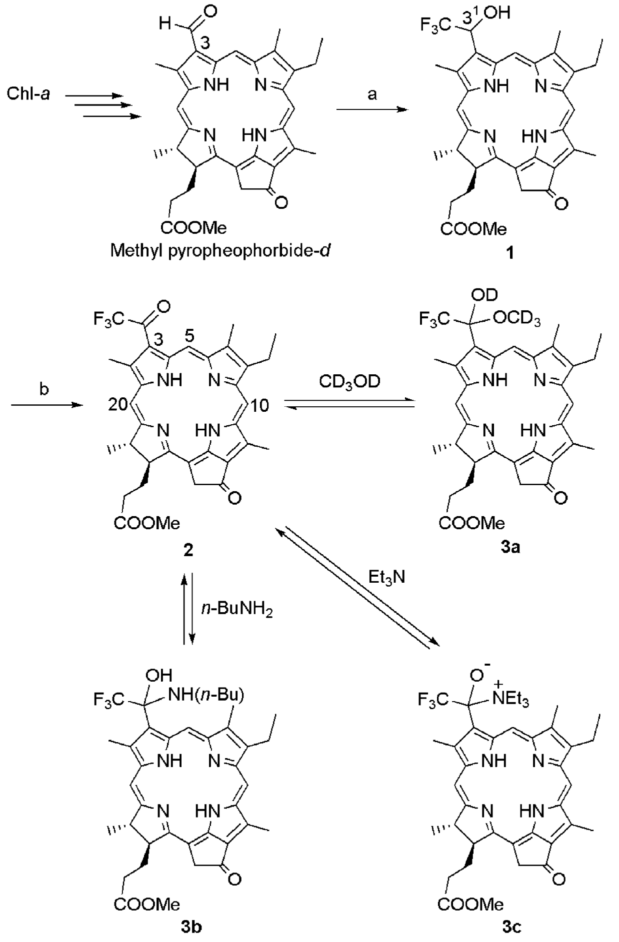
Synthesis of trifluoroacetyl-chlorin **2** and its sensing mechanism are outlined in Scheme 1. The 3-formyl group of methyl pyropheophorbide-*d*[12] was treated with $TMSCF_3$ and the resulting silyl ether was cleaved by aq HCl[13] to give chlorin **1** in 46% yield. Oxidation of the 3^1-hydroxy group in **1** to the 3-carbonyl group in **2** was performed by Pr_4NRuO_4 and 4-methylmorpholine-*N*-oxide.[14] The trifluoroacetyl group of **2** can form adducts as its hemiacetal with an alcohol (**3a**), as its hemiaminal with a primary (or secondary) amine (**3b**), or as its zwitter ion with a tertiary amine (**3c**). Complete conversion from **2** to **3a** in CD_3OD was confirmed by their ^1H and ^{19}F NMR spectra. For example, 5- and 10-protons of **2** appeared at 9.69 and 9.29 ppm, respectively, in $CDCl_3$, and turned into pairs of signals at 10.29/10.28 and 9.36/9.35 ppm in $CDCl_3$–CD_3OD (1:1, v/v) due to the formation of a 1:1 epimeric mixture of 3^1-R/S-**3a**. Similarly, a single ^{19}F signal of **2** (−74.24 ppm in

Keywords: Chlorin; Indicator; Macrocycles; Sensing; Tetrapyrrole.

---

* Corresponding author. Fax: +81 77 561 2659; e-mail: tamiaki@se.ritsumei.ac.jp

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.05.026



Scheme 1. Reagents and conditions: (a) (i) TMSCF$_3$, Bu$_4$NF·3H$_2$O, THF, rt, 5 min, (ii) 10% aq HCl, THF, rt, 2 h, 46%; (b) Pr$_4$NRuO$_4$, 4-methylmorpholine-*N*-oxide, CH$_2$Cl$_2$, rt, 3 h, 47%.

CDCl$_3$) changed to a pair (1:1) of signals at −84.08/−84.09 ppm in CDCl$_3$–CD$_3$OD, which were assigned to the 3^1-CF$_3$ of 3^1-epimerically mixed **3a**.

When *n*-BuNH$_2$ was added to a solution of **2** in CDCl$_3$, the ^{1}H NMR spectrum showed signals of both trifluoroacetyl-chlorin **2** and its hemiaminal **3b**. Figure 1 shows the ^{1}H NMR spectra of three kinds of *meso*-protons of **2** in the presence of 10 equiv *n*-BuNH$_2$ in CDCl$_3$ measured at various temperatures. Trifluoroacetyl form was dominant at 40 °C (ratio of **2**/**3b**, $r = 7.7/1$), but the value of r gradually decreased at a lower temperature and completely changed to its hemiaminal form at −40 °C ($r = 0/1$).[15] Thermodynamic parameters for the complexation were calculated as $\Delta H = -48$ kJ mol^{-1} and $\Delta S = -147$ J K^{-1} mol^{-1} based on the van't Hoff plot as shown in Figure 2.[16]

Figure 3 shows the electronic absorption spectra of various solutions of **2** and the absorption maxima are summarized in Table 1. The Q_y peak maximum of **2** at 696 nm in THF moved to 667 nm in MeOH with a visible color change from brown to purple. The hemiacetalization of **2** with bulky 2-PrOH was so slow at room temperature that the trifluoroacetyl form still existed (about 20%) after standing for 1 day.[17]

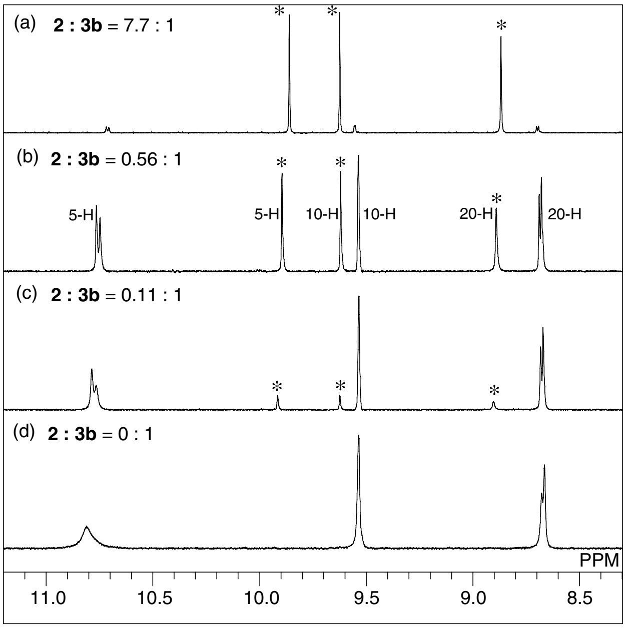


Figure 1. Selected region of the ^{1}H NMR spectra of chlorin **2** in the presence of 10 equiv *n*-BuNH$_2$ in CDCl$_3$ at (a) 40, (b) 0, (c) −20, and (d) −40 °C. *meso*-Protons of the trifluoroacetyl form **2** are indicated by asterisk (∗).

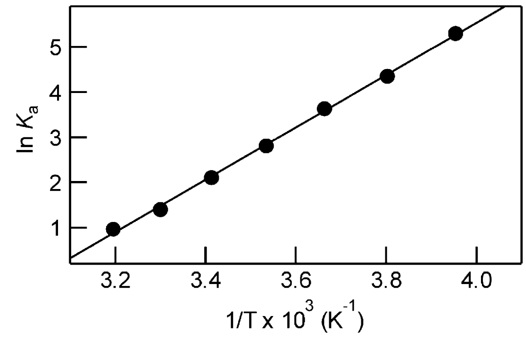


Figure 2. van't Hoff plot of the equilibrium between trifluoroacetyl chlorin **2** and its hemiaminal **3b**. Association constants (K_a = [**3b**]/[**2**][*n*-BuNH$_2$] in CDCl$_3$) were calculated by integration values of their ^{1}H NMR peaks at various temperatures.

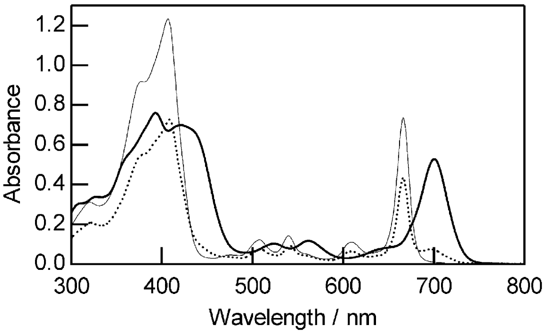


Figure 3. Electronic absorption spectra of chlorin **2** in THF (solid thick line), MeOH (solid thin line), and 2-PrOH (dotted line). [**2**] = 1.0×10^{-5} M. The spectra in THF and MeOH were measured just after preparation of their samples and that in 2-PrOH was done after standing for 1 day at room temperature.

Table 1. Absorption maxima (λ_{max}/nm) of various solvents of **2**

Solvent	Soret	Q_x	Q_y
$CHCl_3$	393, 420	524, 562	701
THF	391, 422	520, 558	696
Toluene	395, 424	525, 563	701
CH_3CN	390, 408	517, 555	693
2-PrOH	408	509, 541	666, 697
MeOH	407	508, 539	667
n-$BuNH_2$	409	508, 539	665
Et_3N	407	507, 536	665

Changes in the electronic absorption and fluorescence emission spectra of **2** by addition of *n*-$BuNH_2$ in THF are shown in Figure 4. The hemiaminal formation required several hours in THF, which is in contrast to the rapid equilibrium in $CDCl_3$. The spectra after reaching the equilibrium showed Q_y peak shift from 696 to 665 nm with several isosbestic points including 422 and 676 nm. The association constant (K_a) was determined to be $7.8 \times 10^3\ M^{-1}$ at 20 °C,[18] much larger than the K_a value of $8\ M^{-1}$ in $CDCl_3$. Polar THF would stabilize the OH/NH groups of hemiaminal **3b** more than $CDCl_3$ does. On the other hand, the K_a value between 4-dimethylamino-4′-trifluoroacetyl-azobenzene and *n*-$BuNH_2$ was reported to be $7.9 \times 10^2\ M^{-1}$ in THF.[8c] In spite of the steric hindrance of 2-CH_3 and 5-H on the chlorin ring, the trifluoroacetyl group of **2** showed this relatively strong binding ability.[19] When excited at 422 nm, a fluorescence intensity at 718 nm decreased with a concomitant increase of the 668 nm emission, which resulted in the ratiometric plot shown in Figure 4b. The K_a value was calculated to be $8.1 \times 10^3\ M^{-1}$ following the fluorescence intensity changes, almost the same value based on the absorption spectra.

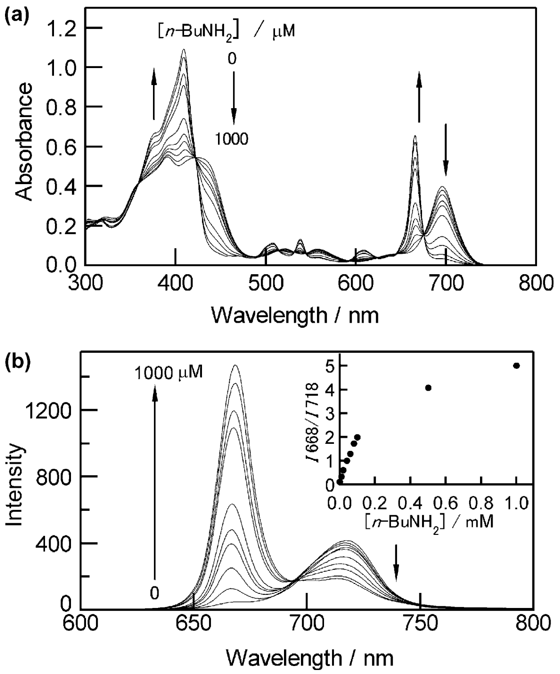


Figure 4. (a) Electronic absorption and (b) fluorescence emission spectral changes of chlorin **2** by addition of *n*-$BuNH_2$ in THF. [**2**] = 1.0×10^{-5} M. Each sample was measured after standing for 24 h at room temperature in the dark. Excited wavelength, 422 nm. Inserted plot represents the relation between the amount of added *n*-$BuNH_2$ and the ratio of fluorescence intensity at 668 and 718 nm.

In summary, we demonstrated a first example of a chlorophyll-based chemosensor. Colorimetric and fluorescent ratiometric sensing of *n*-$BuNH_2$ was performed in THF, together with the determination of thermodynamic parameters of the equilibrium in $CDCl_3$. Introduction of trifluoroacetyl group to other positions on the chlorin macrocycle and the synthesis of bacteriochlorin-based sensors are in progress.

Acknowledgements

This work was partially supported by Grants-in-Aid for Scientific Research (No. 17029065) on Priority Areas (417) from the Ministry of Education, Culture, Sports, Science, and Technology (MEXT) of the Japanese Government and for Scientific Research (B) (No. 15350107) from the Japan Society for the Promotion of Science (JSPS), as well as by the 'Academic Frontier' Project for Private Universities: matching fund subsidy from MEXT, 2003–2007.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.05.026.

References and notes

1. As recent reviews; (a) Suksai, C.; Tuntulani, T. *Chem. Soc. Rev.* **2003**, *32*, 192; (b) Martinez-Manez, R.; Sancenon, F. *Chem. Rev.* **2003**, *103*, 4419; (c) Bell, T. W.; Hext, N. M. *Chem. Soc. Rev.* **2004**, *33*, 589.
2. Scheer, H. In *Light-Harvesting Antennas in Photosynthesis*; Green, B. R., Parson, W. W., Eds.; Kluwer Academic: Dordrecht, 2003; pp 29–81.
3. Recent reviews about synthetic chlorophyll derivatives: (a) Miyatake, T.; Tamiaki, H. *J. Photochem. Photobiol. C: Photochem. Rev.* **2005**, *6*, 89; (b) Balaban, T. S. *Acc. Chem. Res.* **2005**, *38*, 612; (c) Balaban, T. S.; Tamiaki, H.; Holzwarth, A. R. *Topics Curr. Chem.* **2005**, *258*, 1; (d) Tamiaki, H. *Photochem. Photobiol. Sci.* **2005**, *4*, 675.
4. Tamiaki, H.; Amakawa, M.; Shimono, Y.; Tanikaga, R.; Holzwarth, A. R.; Schaffner, K. *Photochem. Photobiol.* **1996**, *63*, 92.
5. Bühlmann, P.; Pretsch, E.; Bakker, E. *Chem. Rev.* **1998**, *98*, 1593.
6. (a) Lee, H. J.; Yoon, I. J.; Yoo, C. L.; Pyun, H.-J.; Cha, G. S.; Nam, H. *Anal. Chem.* **2000**, *72*, 4694; (b) Makarychev-Mikhailov, S.; Goryacheva, O.; Mortensen, J.; Legin, A.; Levitchev, S.; Vlasov, Y. *Electroanalysis* **2003**, *15*, 1291.
7. (a) Mohr, G. J.; Citterio, D.; Demuth, C.; Fehlmann, M.; Jenny, L.; Lohse, C.; Moradian, A.; Nezel, T.; Rothmaier, M.; Spichiger, U. E. *J. Mater. Chem.* **1999**, *9*, 2259; (b) Mohr, G. J. *Sens. Actuators B* **2003**, *90*, 31.
8. (a) Mohr, G. J.; Demuth, C.; Spichiger-Keller, U. E. *Anal. Chem.* **1998**, *70*, 3868; (b) Mohr, G. J.; Tirelli, N.; Lohse, C.; Spichiger-Keller, U. E. *Adv. Mater.* **1998**, *10*, 1353; (c) Mertz, E.; Beil, J. B.; Zimmerman, S. C. *Org. Lett.* **2003**, *5*,

3127; (d) Mertz, E.; Zimmerman, S. C. *J. Am. Chem. Soc.* **2003**, *125*, 3424; (e) Mertz, E.; Elmer, S. L.; Balija, A. M.; Zimmerman, S. C. *Tetrahedron* **2004**, *60*, 11191; (f) Matsui, M.; Yamada, K.; Funabiki, K. *Tetrahedron* **2005**, *61*, 4671.

9. (a) Kim, Y. K.; Lee, Y.-H.; Lee, H.-Y.; Kim, M. K.; Cha, G. S.; Ahn, K. H. *Org. Lett.* **2003**, *5*, 4003; (b) Chung, Y. M.; Raman, B.; Kim, D.-S.; Ahn, K. H. *Chem. Commun.* **2006**, 186.
10. (a) Sasaki, S.; Hashizume, A.; Citterio, D.; Fujii, E.; Suzuki, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 3005; (b) Sasaki, S.; Monma, G.; Citterio, D.; Yamada, K.; Suzuki, K. *Chimia* **2005**, *59*, 204.
11. Recent examples of ratiometric fluorescent chemosensors; (a) Kubo, Y.; Yamamoto, M.; Ikeda, M.; Takeuchi, M.; Shinkai, S.; Yamaguchi, S.; Tamao, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 2036; (b) Charier, S.; Ruel, O.; Baudin, J.-B.; Alcor, D.; Allemand, J.-F.; Meglio, A.; Jullien, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 4785; (c) Liu, B.; Tian, H. *Chem. Commun.* **2005**, 3156; (d) Peng, X.; Wu, Y.; Fan, J.; Tian, M.; Han, K. *J. Org. Chem.* **2005**, *70*, 10524; (e) Baruah, M.; Qin, W.; Vallée, R. A. L.; Beljonne, D.; Rohand, T.; Dehaen, W.; Boens, N. *Org. Lett.* **2005**, *7*, 4377; (f) Ajayaghosh, A.; Carol, P.; Sreejith, S. *J. Am. Chem. Soc.* **2005**, *127*, 14962.
12. Tamiaki, H.; Miyata, S.; Kureishi, Y.; Tanikaga, R. *Tetrahedron* **1996**, *52*, 12421.
13. (a) Li, G.; Chen, Y.; Missert, J. R.; Rungta, A.; Dougherty, T. J.; Grossman, Z. D.; Pandey, R. K. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1785; (b) Singh, R. P.; Shreeve, J. M. *Tetrahedron* **2000**, *56*, 7613.
14. (a) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639; (b) Tamiaki, H.; Yagai, S.; Miyatake, T. *Bioorg. Med. Chem.* **1998**, *6*, 2171.
15. In the presence of 10 equiv MeOH in $CDCl_3$, only 2% of **2** existed as its hemiacetal form at 20 °C while more basic *n*-$BuNH_2$ showed the value of $r = 2.5/1$ (29% hemiaminal form).
16. Almost the same ΔH and ΔS values for the binding between trifluoroacetophenone derivatives and acetate ion in acetonitrile were reported in Ref. 9a, where thermodynamic data were determined by isothermal titration calorimetry (ITC).
17. A similar time-dependent spectral change of hemiaminal formation of 4-dimethylamino-4′-(perfluoropropanoyl)-azobenzene in 2-methyl-1-propanol was described in Ref. 8f. For the time-dependent spectral change of chlorin **2** in 2-PrOH, see Figure S5.
18. Hirose, K. *J. Incl. Phenom. Macrocycl. Chem.* **2001**, *39*, 193.
19. The higher K_a value of **2** might be ascribable to the stronger electron-withdrawing ability of chlorin macrocycle compared to azobenzene moiety. For substituent effects on trifluoroacetophenone derivatives, see Refs. 10a and 20.
20. Behringer, C.; Lehmann, B.; Haug, J.-P.; Seiler, K.; Morf, W. E.; Hartman, K.; Simon, W. *Anal. Chim. Acta* **1990**, *233*, 41.