N-Methylporphyrin as a Binding Motif for the Recognition of a Phenolic Hydroxy Group

Satoshi Kotomari,[1] Tsukasa Yoshikawa,[1] Tadashi Mizutani,*[1] and Hideki Takagi[2]
[1]*Department of Molecular Science and Technology, Faculty of Engineering, Doshisha University, Kyotanabe, Kyoto 610-0321*
[2]*Toyota Central Research and Development Laboratories, Inc., Yokomichi, Nagakute, Aichi-gun, Aichi 480-1192*

(Received June 20, 2006; CL-060699; E-mail: tmizutan@mail.doshisha.ac.jp)

Binding of phenols to *N*-methyltetraphenylporphyrin **1** was investigated in dichloromethane. The binding constant of 4-nonylphenol to **1** was 3200 M^{-1} while that to simple amine, diamine and triamine were less than 100 M^{-1} at 25 °C. **1** showed tight binding to ortho-substituted phenols, and the binding constant to 2,6-xylenol was 710,000 M^{-1}.

X-ray crystallographic studies of binding of estrogen to the estrogen receptor showed that the phenolic hydroxy group is hydrogen bonded to the carboxylate group of the glutamic acid side chain of the protein, and the hydrogen bond is assisted by several auxiliary hydrogen bonds, which would either fix the interacting atoms or strengthen electronic polarization.[1] Development of a synthetic receptor for phenols is an important topic of investigations,[2] particularly in relation to the environmental issue of endocrine-disrupting materials.[3] We report the use of amines as a basic hydrogen-bonding site for recognition of phenolic hydroxy groups. *N*-Alkylporphyrins and saddle-shaped porphyrins showed unusual electronic properties, and have been studied recently.[4] We demonstrate that *N*-methylporphyrin is a better phenol receptor than simple mono-, di-, and triamines.

N-Methyl-5,10,15,20-tetraphenylporphyrin (**1**) was prepared by the reaction of 5,10,15,20-tetraphenylporphyrin (TPP) with methyl fluorosulfonate (Scheme 1).[5] The ^{1}H NMR spectrum of **1** in CD_2Cl_2 showed only one resonance in the upfield region at δ −4.08 ppm (ca. 2H) at 25 °C,[6] but upon cooling to −80 °C, two sharp singlet resonances appeared at −2.44 ppm (1H) and −4.29 ppm (3H), which can be ascribed to the inner NH proton and the *N*-Me protons, respectively. Therefore, the ^{1}H NMR spectrum recorded at room temperature was complicated due to the chemical exchange process, and lowering temperature disrupted it to simplify the spectrum.

Binding of phenols to **1**–**8** was investigated by UV–vis titration and variable-temperature NMR. In UV–vis titration, changes in the Soret band of **1** were monitored as a function of phenol concentrations, or changes in the phenol absorption were monitored as a function of the amine concentrations. In Figure 1 are shown the UV–vis spectral changes of **1** upon addition of 4-nonylphenol. The decrease in absorbance at 433 nm and the increase at 446 nm were observed. Similar spectral changes were observed for other phenols. For **1**, the binding isotherm was fitted on the basis of sequential 1:1 and 1:2 (host/guest) binding equilibria, and binding constants K_1 and K_2 were determined (Table 1). For mono-, di-, and triamines, the binding constants were smaller, and only the binding constants for the 1:1 complex were determined. The binding constants of *p*-nonylphenol by **2**–**8** in $CHCl_3$ at 25 °C were 27 (**2**), 71 (**3**), 33 (**4**), 45 (**5**), 86 (**6**), 68 (**7**), and 22 M^{-1} (**8**).

Binding constants of phenols by **1** were on the order of 10^3 to 10^4 M^{-1}, while those by mono-, di-, and triamines were less than 100 M^{-1}. It is noteworthy that the parent phenol and phenols with electron-donating substituents were bound to **1** with moderate affinity. In the previous paper, we reported that 5-quinolylporphyrin bound phenol with the binding constant of 5 M^{-1}.[2h] Similarly, binding of phenols to chiral diamines

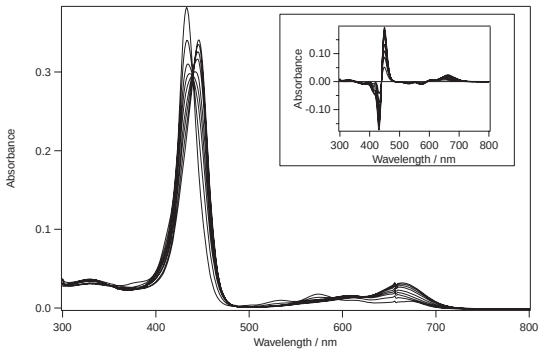
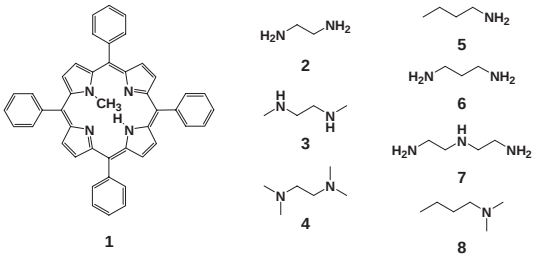


Figure 1. UV–vis titration of **1** with 4-nonylphenol in CH_2Cl_2 at 25 °C. Difference spectra (inset).

Table 1. Binding constants of phenols to *N*-methyl-5,10,15,20-tetraphenylporphyrin (**1**) in CH_2Cl_2 at 25 °C[a]

Phenols	K_1/M^{-1} (standard deviations)
Phenol	20,000 (2000)
4-Methylphenol	18,000 (1000)
4-Ethylphenol	9300 (600)
4-Nonylphenol	3200 (300)
4-Chlorophenol	5200 (700)
4-Bromophenol	4300 (300)
4-Cyanophenol	237,000 (13,000)
2-Methylphenol	12,000 (2000)
2-Ethylphenol	5200 (400)
2-Cyanophenol	24,000 (700)
2,6-Xylenol	710,000 (40,000)

[a]The values of K_2 were smaller, and typically K_1/K_2 was 20 or larger except for 4-nonylphenol: K_2 = 1300 M^{-1}.



Scheme 1. Structures of phenol receptors.

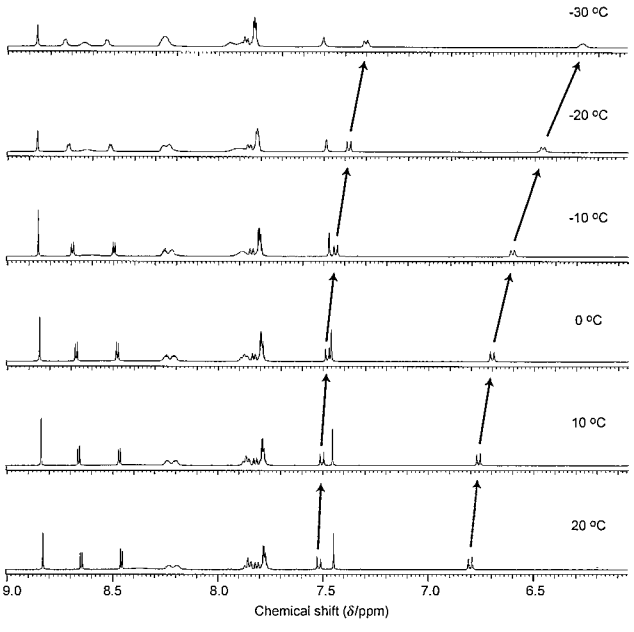


Figure 2. ^{1}H NMR spectra of **1** (2.0×10^{-3} M) and *p*-cyanophenol (1.0×10^{-3} M) in CD_2Cl_2 at -30, -20, -10, 0, 10, and 20 °C.

was investigated, and only the phenols with electron-withdrawing groups or biphenyldiol were bound to the chiral diamine with significant binding affinity.[7] In a control experiment, UV–vis titration with TPP and phenols was investigated, but no spectral changes were observed. Thus, receptor **1** showed tighter binding to phenols than the simple amines and the parent porphyrin. Effects of ortho-substituents were unpredictable. Only weak steric inhibition of binding was seen for the ortho-substituted phenols. Unexpectedly, 2,6-xylenol was bound to **1** with a large binding constant of 710,000 M^{-1}. Molecular modeling studies indicated that one of the methyl groups was close to the porphyrin core and CH/π interactions[8] may play a significant role.

^{1}H NMR studies supported the binding of phenols to **1**. In Figure 2 are shown ^{1}H NMR spectra of 2×10^{-3} M of **1** and 1×10^{-3} M of 4-cyanophenol in CD_2Cl_2. The resonance of 2-H of 4-cyanophenol, which appeared at 6.92 ppm in the absence of **1**, shifted upfield upon cooling, and appeared at 6.28 ppm at -30 °C. Similar but smaller upfield shift of the 3-H resonance of 4-cyanophenol was observed. These resonance displacements can be attributed to the ring-current effects of the porphyrin, and are consistent with the hydrogen bonding of the OH group to the pyrrolic nitrogen. We reported that lowering temperature induced proton transfer in the hydrogen-bonding complex between phenol and amine, and consequently caused changes in the dynamics in the complex.[9] The upfield shift of the guest aromatic resonances in the complex between **1** and 4-cyanophenol implies that fluctuation of the guest was suppressed upon cooling to form a rigid host–guest complex.

The acid dissociation constant (pK_3) of **1** was reported to be 5.64 in nitrobenzene, while that of TPP be 4.38.[5] The increased basicity of **1** was attributed to the bending of the porphyrin nucleus by the central methyl group, which leads to the localized lone-pair electrons on the nitrogen atoms available for the hydrogen bonding with phenols. It is puzzling, however, that the basicity of **1** is much weaker than simple amines (**2**–**5**), and yet the binding of phenols by **1** was tighter. One possible explanation may be solvation or reorganization energy of the solvent. The lone-pair electrons of simple amines are localized and subjected to solvation, while the lone-pair electrons of **1** should be delocalized and **1** can be polarized only when the phenol was bound to **1**. This mechanism would reduce the solvation of the basic recognition site of **1** to enhance the binding free energy.

In conclusion, we demonstrated that *N*-methylporphyrin acts as a phenol receptor, where both hydrogen-bonding and CH/π interactions played a significant role.

We thank Dr. Yasuhisa Kuroda of Kyoto Institute of Technology for providing us the computer program for curve fitting. One of the authors, TM, thanks the financial aid from Doshisha University's Research Promotion Fund.

References

1 D. M. Tanenbaum, Y. Wang, S. P. Williams, P. B. Sigler, *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 5998.
2 a) L. Guilleux, P. Krausz, L. Nadjo, R. Uzan, C. Giannotti, *J. Chem. Soc., Perkin Trans. 2* **1984**, 475. b) J. L. Sessler, T. D. Mody, V. Lynch, *J. Am. Chem. Soc.* **1993**, *115*, 3346. c) B. J. Whitlock, W. H. Whitlock, *J. Am. Chem. Soc.* **1994**, *116*, 2301. d) R. J. Jansen, R. de Gelder, A. E. Rowan, H. W. Scheeren, R. J. M. Nolte, *J. Org. Chem.* **2001**, *66*, 2643. e) M. Narita, N. Dorjpalam, K. Teranishi, F. Hamada, *Anal. Sci.* **2002**, *18*, 711. f) K. Inumaru, Y. Inoue, S. Kakii, T. Nakano, S. Yamanaka, *Chem. Lett.* **2003**, *32*, 1110. g) Y. Kanekiyo, R. Naganawa, H. Tao, *Angew. Chem., Int. Ed.* **2003**, *42*, 3014. h) K. Wada, T. Mizutani, S. Kitagawa, *J. Org. Chem.* **2003**, *68*, 5123. i) J. M. C. A. Kerckhoffs, T. Ishi-i, V. Paraschiv, P. Timmerman, M. Crego-Calama, S. Shinkai, D. N. Reinhoudt, *Org. Biomol. Chem.* **2003**, *1*, 2596. j) T. Ikegami, W.-S. Lee, H. Nariai, T. Takeuchi, *J. Chromatogr., B* **2004**, *804*, 197. k) M. G. J. ten Cate, D. N. Reinhoudt, M. Crego-Calama, *J. Org. Chem.* **2005**, *70*, 8443.
3 a) G. C. Mueller, U.-H. Kim, *Endocrinology* **1978**, *102*, 1429. b) J. A. McLachlan, *Endocr. Rev.* **2001**, *22*, 319.
4 a) A. H. Jackson, G. R. Dearden, *Ann. N.Y. Acad. Sci.* **1973**, *206*, 151. b) H. J. Callot, *Tetrahedron Lett.* **1979**, 3093. c) H. Kubo, T. Aida, S. Inoue, Y. Okamoto, *J. Chem. Soc., Chem. Commun.* **1988**, 1015. d) I. Artaud, N. Gregoire, J. P. Battioni, D. Dupre, D. Mansuy, *J. Am. Chem. Soc.* **1988**, *110*, 8714. e) A. L. Balch, C. R. Cornman, L. Latos-Grazynski, M. M. Olmstead, *J. Am. Chem. Soc.* **1990**, *112*, 7552. f) K. M. Barkigia, M. D. Berber, J. Fajer, C. J. Medforth, M. W. Renner, K. M. Smith, *J. Am. Chem. Soc.* **1990**, *112*, 8851. g) M. O. Senge, W. W. Kalisch, R. Steffen, *Liebigs Ann./Rec.* **1997**, 1345. h) Y. Furusho, T. Kimura, Y. Mizuno, T. Aida, *J. Am. Chem. Soc.* **1997**, *119*, 5267.
5 D. K. Lavallee, A. E. Gebala, *Inorg. Chem.* **1974**, *13*, 2004.
6 H. M. G. Al-Hazimi, A. H. Jackson, A. W. Johnson, M. Winter, *J. Chem. Soc., Perkin Trans. 1* **1977**, 98.
7 T. Mizutani, H. Takagi, Y. Ueno, K. Yamamura, H. Ogoshi, *J. Phys. Org. Chem.* **1998**, *11*, 737.
8 a) M. Nishio, *Tetrahedron* **2005**, *61*, 6923. b) T. Mizutani, K. Wada, S. Kitagawa, *J. Org. Chem.* **2000**, *65*, 6097. c) Y. Kuroda, Y. Kato, M. Ito, J. Hasegawa, H. Ogoshi, *J. Am. Chem. Soc.* **1994**, *116*, 10338. d) K. Kobayashi, Y. Asakawa, Y. Kikuchi, H. Toi, Y. Aoyama, *J. Am. Chem. Soc.* **1993**, *115*, 2648.
9 H. Takagi, T. Mizutani, T. Horiguchi, S. Kitagawa, H. Ogoshi, *Org. Biomol. Chem.* **2005**, *3*, 2091.

Published on the web (Advance View) August 5, 2006; doi:10.1246/cl.2006.1020