Molecular Trench: Highly Complementary Binding Sites for Tartaric Acid Dialkyl Ester

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Recognition of shapes of molecules based on multiple intermolecular interactions is of current interest in biomimetic chemistry.[1] During the course of our attempts to construct molecular recognition sites on porphyrin molecules, we have demonstrated that porphyrins may also provide excellent core frameworks for various types of multipoint recognition sites, including two-, three-, and four-point recognition systems.[2] In this paper, we report a unique trenchtype binding site on a porphyrin which specifically recognizes tartaric acid derivatives with four-point hydrogen bonding.

The new receptor **1** was synthesized via the double bridging reaction of $\alpha,\alpha,\alpha,\alpha$-*meso*-tetrakis(*o*-aminophenyl)porphyrin with 4-nitroisophthalic acid dichloride as shown in Scheme 1. The product was purified on a usual silica gel column (benzene/Et_2O = 1/1) to give meso (**1a**) and chiral (**1b** (+ and −)) isomers. The similar bridged porphyrins, **2**, **3**, and **4**, are also prepared via a similar reaction using diacid chlorides of 5-nitro-, unsubstituted, and 4,6-dinitroisophthalic acid, respectively.[3] The space-filling molecular models of these porphyrins show that two benzene rings form a trenchlike space of ca. 5–7 Å depth on the porphyrin plane. We found that tartaric acid derivatives were bound into the trench space surrounded by four amide bonds capable of hydrogen bonding. Titration experiments using electronic spectra demonstrate that the present recognition is quite sensitive toward the shapes of substrates (Table 1). As seen in Table 1, the present binding is highly specific toward tartaric acid diesters, and no combination of two functional groups corresponding to the partial structure of tartaric acid results in appreciable recognition by **1a**. It should be noted that even diethyl malate, which lacks only one hydroxyl moiety compared with diethyl tartrate, exhibits very weak complex formation behavior. Furthermore, **1a** can significantly recognize the configuration of tartaric acid, i.e., the association constant for diethyl L-tartrate is 4500 M^{-1}, while that for the meso isomer is only 530 M^{-1}. Another interesting feature of the present recognition is the unexpected steric effect of the ester part of the substrates. Comparisons of association constants for dimethyl, diethyl, diisopropyl, and di-*sec*-butyl tartrates indicate that a bulkier substrate is recognized more strongly in the present recognition system. However, di-*tert*-butyl tartrate seems to be too bulky for the binding site of **1**.[4] On the other hand, present recognition seems to be insensitive toward the configuration of **1**, i.e., observed association constants between **1a**, (+)-**1b**, and (−)-**1b** and diethyl L-tartrate are 4000, 4500, and 3900 M^{-1}, respectively.

Detailed information about the structure of the present complex was obtained from ^1H NMR spectroscopic investigations. Although ^1H NMR signals of the guest significantly broaden in the presence of the host at room temperature, the signals remarkably sharpen at low temperature, and each free and bound guest gives clearly separated signals at −40 °C as shown in Figure 1, where diisopropyl L-tartrate was employed as the guest. The resonances of the guest show significant upfield shifts and lose their C_2 symmetric character upon complexation. The most

Scheme 1

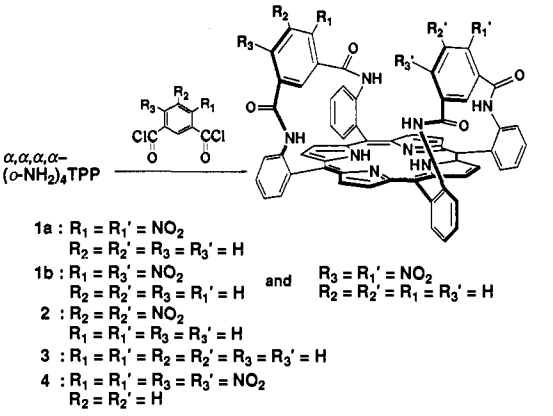
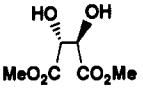
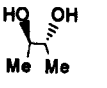
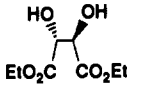
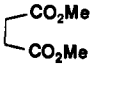
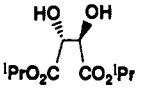
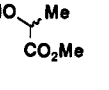
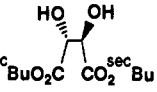
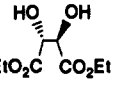
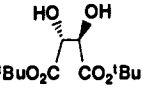
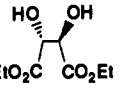
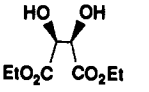
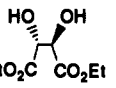
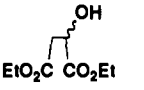


Table 1. Association Constants between Bridged Porphyrins and Tartrate Derivatives[a]

host	guest	K_a (M)[b]	host	guest	K_a (M)[b]
1a		2 700	**1a**		9.1
1a		4 500	**1a**		*c*
1a		22 000	**1a**		*c*
1a		24 000	**2**		144
1a		5 060	**3**		36
1a		530	**4**		1.6×10^5
1a		7.1			

[a] In $CHCl_3$, at 15 °C. [b] Standard deviation, <9%. [c] No appreciable binding was observed.

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(1) See, for example: (a) Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1009. (b) Lehn, J.-M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 89. (c) Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 245. (d) *Biomimetic Chemistry*; Dolphin, D., McKenna, C., Murakami, Y., Tabushi, I., Eds.; American Chemical Society: Washington, DC, 1980; Vol. 191. (e) Dugas, H. In *Bioorganic Chemistry*, 2nd ed.; Cantor, C. R., Ed.; Springer-Verlag: New York, 1989. (f) *Inclusion Phenomena and Molecular Recognition*; Atwood, J. L., Ed.; Plenum Press: New York, 1990. (g) Vögtle, F. *Supramolecular Chemistry*; John Wiley & Sons: Chichester, 1991.

(2) For two-point system, see: (a) Aoyama, Y.; Yamagishi, A.; Asagawa, M.; Toi, H.; Ogoshi, H. *J. Am. Chem. Soc.* **1988**, *110*, 4076. (b) Aoyama, Y.; Asakawa, M.; Yamagishi, A.; Toi, H.; Ogoshi, H. *J. Am. Chem. Soc.* **1990**, *112*, 3145. (c) Aoyama, Y.; Asakawa, M.; Matsui, Y.; Ogoshi, H. *J. Am. Chem. Soc.* **1991**, *113*, 6233. For three-point system, see: (d) Kuroda, Y.; Kato, Y.; Higashioji, T.; Ogoshi, H. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 723. For four-point system, see: (e) Hayashi, T.; Miyahara, T.; Hashizume, N.; Ogoshi, H. *J. Am. Chem. Soc.* **1993**, *115*, 2049.

(3) Bridged porphyrins **1** and **4** are newly synthesized in this work. The chiral isomers, (+)-**1b** and (−)-**1b**, were resolved by a chiral HPLC column. Detailed spectroscopic data for these porphyrins are available as supplementary material. Bridged porphyrins **2** and **3** had been prepared by Collman et al., see: (a) Collman, J. P.; Brauman, J. I.; Fitzgerald, J. P.; Hampton, P. D.; Naruta, Y.; Michida, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 47. (b) Collman, J. P.; Gagne, R. R.; Reed, C. A.; Halbert, T. R.; Lang, G.; Robinson, W. T. *J. Am. Chem. Soc.* **1975**, *97*, 1427.

(4) The origin of this very interesting selectivity is not clear at present. However, the observed behavior of binding constants for various alkyl tartrates and consideration of molecular modeling of the present molecular trench strongly suggest that van der Waals contact between the porphyrin surface and the alkyl groups determines present selectivity.

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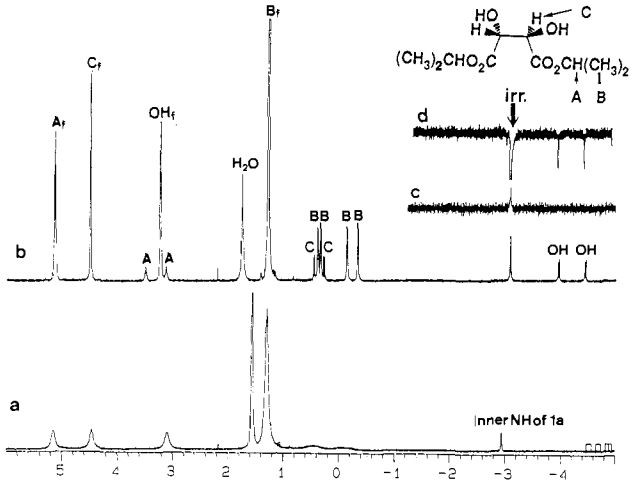


Figure 1. ^{1}H NMR spectra (500 MHz) of diisopropyl L-tartrate in the presence of **1a** in $CDCl_3$ ([**1a**] = 9.9×10^{-4} M, [diisopropyl L-tartrate] = 3×10^{-3} M) (a) at 23.8 °C, (b) at −50 °C, (c) at −50 °C in the presence of D_2O, (d) difference NOE spectra at −50 °C obtained by irradiation at −3.1 ppm. Each signal was assigned as A, B, C, and OH, which correspond to the protons of the tartrate in the inset, and the suffix "f" indicates the signals of free guest.

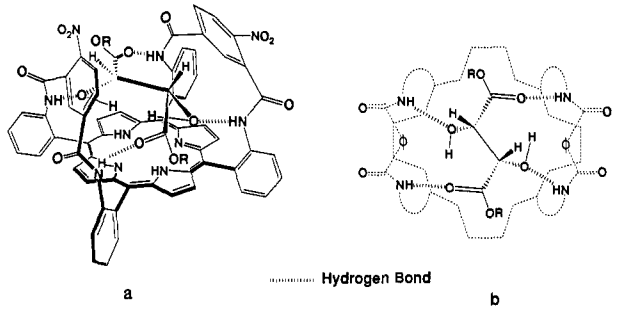
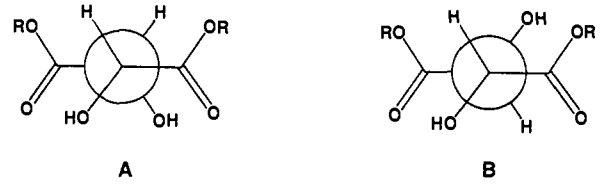


Figure 2. (a) Schematic structure of the complex of **1b** with dialkyl tartrate. (b) Relative position of alkyl tartrate on the porphyrin plane and the hydrogen bond network in the complex.

interesting observation in these spectra is extraordinary upfield shifts of two hydroxyl protons of the bound guest. These protons exhibited clear coupling with vicinal CH protons and were observed at δ −3.98 and −4.46 ppm, respectively. Irradiation of porphyrin inner-NH protons of **1a** observed at δ −3.11 ppm results in nuclear Overhauser enhancements of these hydroxyl proton signals, which reveals close contact of these two kinds of protons. Furthermore, the coupling constant between central vicinal protons of the guest at δ 0.26 and 0.44 ppm becomes observable to be 1.4 Hz because of the lack of symmetry of the guest in the complex. The application of the Karplus's relationships to the observed coupling constant suggests a gauche configuration of these protons.[5]

The participation of hydrogen bonding in the present complexation is confirmed by NMR and IR spectroscopic titration. For example, amide NH protons of **1a** at δ 7.18 and 7.99 ppm show significant downfield shifts on addition of diethyl L-tartrate. Interestingly, addition of an increasing amount of the guest caused loss of σ symmetry of **1a**, and these amide protons shifted separately to appear at δ 7.39, 7.40, 8.37, and 8.48 ppm on complexation. In the IR spectra of **1a**, absorption of amide NH is observed at 3403 cm^{-1}. On addition of diisopropyl L-tartrate, a new absorption band appears at 3340 cm^{-1}, and the original absorption almost disappears in the presence of 1.7 times excess of the substrate. These observations strongly indicate that all four amide protons in **1a** participate in the present complexation as proton donor sources for hydrogen bonding.

The most plausible structures of the present porphyrin–tartrate complex derived from these observations are shown in Figure 2. In this complex, the guest molecule is bound via two NH···O=C and two NH···OH hydrogen bonds so as to make close contact between two hydroxyl groups of the guest and the porphyrin surface. It should be noted that the conformation of bound L-tartrate (**A**) is essentially the same as one of its preferred conformations, gauche OH/OH, gauche H/H, and anti CO_2R/CO_2R, in which two carbonyl and two hydroxyl oxygen atoms exist practically in a plane.[6] Thus, weak binding of the meso



tartrate (**B**) may be explained by the fact that this isomer has no such structure which can satisfy these configurations simultaneously.

Another interesting aspect of the present molecular recognition is the effect of nitro groups on complex formation. Although the relative configuration of two nitro groups in **1**, meso or optically active configuration, does not affect the present molecular recognition, the existence of nitro groups at the 4 position of the bridging benzene is essential for present recognition, i.e., the 5-nitro isomer, **3**, and unsubstituted derivative, **2**, showed 30 and 100 times weaker binding toward diethyl L-tartrate, respectively (Table 1). This remarkable effect of the nitro groups on the bridging benzene indicates that the present hydrogen-bonding system is significantly affected by the electronic effect of 4-nitro groups, which enhances the proton donor ability of the amide NH at the ortho position.[7] These observations lead us to prepare an improved host, **4**, doubly bridged with 4,6–dinitroisophthalic acid, which is expected to exhibit extremely strong affinities toward tartrate derivatives. As expected, the preliminary titration experiments show the binding constant of **4** with diethyl tartrate and diisopropyl tartrate to be 1.6×10^5 and 1.4×10^6 M^{-1}, respectively. Thus, the present molecular recognition system provides a unique "tunable hydrogen-bonding site".

Supplementary Material Available: ^{1}H NMR, MS, IR, and UV–vis data for the new porphyrins (**1a**, **1b**, and **4**), circular dichroism data of chiral **1** and data on spectroscopic titration by UV, IR, and NMR spectroscopies (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(5) (a) Karplus, M. *J. Chem. Phys.* **1959**, *30*, 11. (b) Karplus, M. *J. Phys. Chem.* **1961**, *64*, 1793. (c) Karplus, M. *J. Am. Chem. Soc.* **1963**, *85*, 2870. (d) Jackman, L. M.; Sternhell, S. *Applications of nuclear magnetic resonance spectroscopy in organic chemistry*, 2nd ed.; Barton, D. H. R., Doering, W., Eds.; Pergamon Press: Oxford, 1969; p 280.

(6) (a) Hasan, M. u. *Org. Magn. Reson.* **1980**, *14*, 309. (b) Polavarapu, P. L.; Ewig, C. S.; Chandramouly, T. *J. Am. Chem. Soc.* **1987**, *109*, 7382. (c) Egli, M.; Dobler, M. *Helv. Chim. Acta* **1989**, 72, 1135.

(7) In the isophthalic acid derivatives, only carboxylic acid at the ortho position of the nitro group shows a significant decrease of the pK_a value, see: Wegsheider, R. *Monatsh. Chem.* **1916**, *37*, 219; *J. Chem. Soc.* **1916**, *110*, 467.