JOC Article

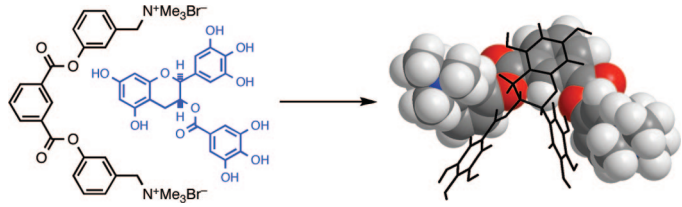
A Water-Soluble Acyclic Phane Receptor Recognizing 2,3-*trans*-Gallate-Type Catechins

Nobuyuki Hayashi* and Tomomi Ujihara

National Institute of Vegetable and Tea Science, 2769 Kanaya, Shimada, Shizuoka 428-8501, Japan

hayn@affrc.go.jp

Received February 19, 2008



To recognize gallate-type catechins in aqueous solution, two water-soluble acyclic phane receptors containing three aromatic rings were synthesized. The binding of these receptors to eight catechin analogues was investigated with ^{1}H NMR spectroscopy. The stoichiometric ratios of the complexes between the receptors and the catechins were 1:1 in every case. The binding abilities were estimated by ^{1}H NMR titration. The meta-substituted receptor showed excellent binding ability for the 2,3-*trans*-gallate-type catechins. This study revealed that a simple acyclic phane receptor can distinguish differences in the structures of the catechin analogues.

Introduction

Catechins, found in the leaves and buds of the tea plant (*Camellia sinensis*), are polyphenolic compounds which have attracted a great deal of attention because of their various physiologically modulating effects.[1] The strength of these bioactivities is closely related to the chemical structures of the catechin molecules. As shown in Figure 1, the eight major catechins in green tea are classified into four categories by the existence of a galloyl group on the oxygen atom at the C3 position and the relative stereochemistry between the C2 and C3 positions: (1) 2,3-*cis*-gallate-type (**1** and **2**); (2) 2,3-*trans*-gallate-type (**3** and **4**); (3) 2,3-*cis*-nongallate-type (**5** and **6**); and (4) 2,3-*trans*-nongallate-type (**7** and **8**). Generally, the gallate-type catechins show higher activities than the nongallate-type catechins.[2] Therefore, when we aim to develop novel and convenient sensing devices for recognizing catechins using host−guest chemistry, artificial receptors for gallate-type catechins are indispensable.

Molecular recognition of aromatic compounds in aqueous solution has been studied with water-soluble cyclophanes.[3,4] Although acyclic phanes are more easily synthesized than cyclophanes, few studies on acyclic receptors in water have been carried out.[5] Therefore, we embarked on a study of water-soluble acyclic phane receptors for gallate-type catechins. In this paper, the syntheses of the new receptors and the estimation of their

* To whom correspondence should be addressed. Phone: +81-547-45-4982. Fax: +81-547-46-2169.

(1) Hayashi, N.; Ujihara, T. *Tetrahedron* **2007**, *63*, 9802–9809, and see references cited therein.

(2) (a) Okabe, S.; Suganuma, M.; Hayashi, M.; Sueoka, E.; Komori, A.; Fujiki, H. *Jpn. J. Cancer Res.* **1997**, *88*, 639–643. (b) Tezuka, M.; Suzuki, H.; Suzuki, Y.; Hara, Y.; Okada, S. *Jpn. J. Toxicol. Environ. Health* **1997**, *43*, 311–315. (c) Ishikawa, T.; Suzukawa, M.; Ito, T.; Yoshida, H.; Ayaori, M.; Nishiwaki, M.; Yonemura, A.; Hara, Y.; Nakamura, H. *Am. J. Clin. Nutr.* **1997**, *66*, 261–266. (d) Miura, S.; Watanabe, J.; Tomita, T.; Sano, M.; Tomita, I. *Biol. Pharm. Bull.* **1994**, *17*, 1567–1572. (e) Hara, Y.; Watanabe, M. *J. Jpn. Soc. Food Sci. Technol.* **1989**, *36*, 951–955.

(3) Reviews on the water-soluble cyclophanes: (a) Diederich, F. *Modern Cyclophane Chemistry*; Gleiter, R. Ed.; WILEY-VCH Verlag: Weinheim, Germany, 2004; pp 519−546. (b) Odashima, K.; Koga, K. *Comprehensive Supramolecular Chemistry*; Vögtle, F. Ed.; Elsevier Science: Oxford, UK, 1996; Vol. 2, pp 143−194. (c) Murakami, Y.; Kikuchi, J.; Hisaeda, Y.; Hayashida, O. *Chem. Rev.* **1996**, *96*, 721–758. (d) Webb, T. H.; Wilcox, C. S. *Chem. Soc. Rev.* **1993**, 383–395. (e) Seel, C.; Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 528–549. (f) Murakami, Y.; Kikuchi, J.; Hisaeda, Y.; Ohno, T. *Frontiers in Supramolecular Organic Chemistry and Photochemistry*; Schneider, H.-J., Durr, H., Eds.; VCH: Weinheim, Germany, 1991; pp 145−166. (g) Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 362–386. (h) Odashima, K.; Koga, K. *Cyclophanes*; Keehn, P. M., Rosenfeld, R. M. Eds.; Academic Press: New York, 1983; Vol. 2, pp 629−678. (i) Murakami, Y. *Top. Curr. Chem.* **1983**, *115*, 107–155. (j) Tabushi, I.; Yamamura, K. *Top. Curr. Chem.* **1983**, *113*, 145–182.

(4) Articles on the water-soluble calixarenes: (a) Alam, I.; Gutsche, C. D. *J. Org. Chem.* **1990**, *55*, 4487–4489. (b) Shinkai, S.; Shirahama, Y.; Tsubaki, T.; Manabe, O. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1859–1860. (c) Shinkai, S.; Araki, K.; Manabe, O. *J. Am. Chem. Soc.* **1988**, *110*, 7214–7215. (d) Gutsche, C. D.; Alam, I. *Tetrahedron* **1988**, *44*, 4689–4694. (e) Shinkai, S.; Mori, S.; Koreishi, H.; Tsubaki, T.; Manabe, O. *J. Am. Chem. Soc.* **1986**, *108*, 2409–2416. (f) Shinkai, S.; Mori, S.; Tsubaki, T.; Sone, T.; Manabe, O. *Tetrahedron Lett.* **1984**, *25*, 5315–5318.

10.1021/jo800406e CCC: $40.75
Published on Web 06/10/2008

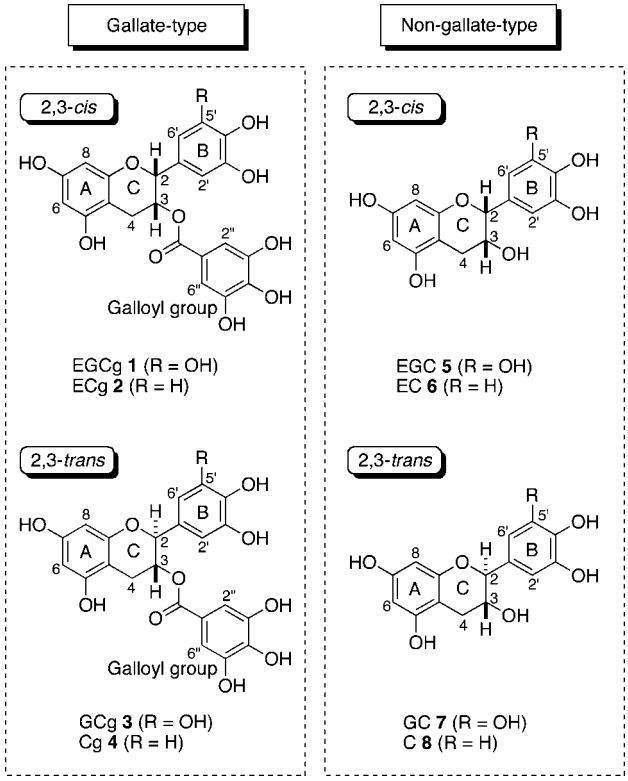


FIGURE 1. Structures of the catechins.

binding abilities in water are described. The binding mechanism is also discussed.

Results and Discussion

The gallate-type catechins and the nongallate-type catechins are composed of three and two aromatic rings, respectively. This structural difference is certain to have a crucial influence on their hydrophobicity. In addition, the relative stereochemistry between C2 and C3 causes a marked difference in the conformations between the *cis*-catechins and the *trans*-catechins. Our concept of an acyclic receptor structure that will recognize catechins is illustrated in Figure 2. A binding site formed from three aromatic rings is expected to interact with the various catechins by different modes. Tetraalkylammonium groups are attached to both side aromatic rings to increase hydrophilicity and to provide steric repulsion that will prevent the side benzene rings from intramolecular association. In the synthesized molecules, the three aromatic rings were linked by ester groups. To examine positional effects of the side benzene rings, meta-substituted isomer **9** and ortho-substituted isomer **10** for the central benzene ring were prepared.

The synthetic pathways are shown in Scheme 1. Isophthaloyl chloride **11** was esterified with 3-hydroxybenzaldehyde, followed by reduction of the formyl groups to give **12**. Bromination of the hydroxy groups of **12** afforded **13**. Bromide **13** was then transformed into the meta-substituted receptor **9** with trimethylamine. The ortho-substituted isomer **10** also was synthesized by using a similar process.

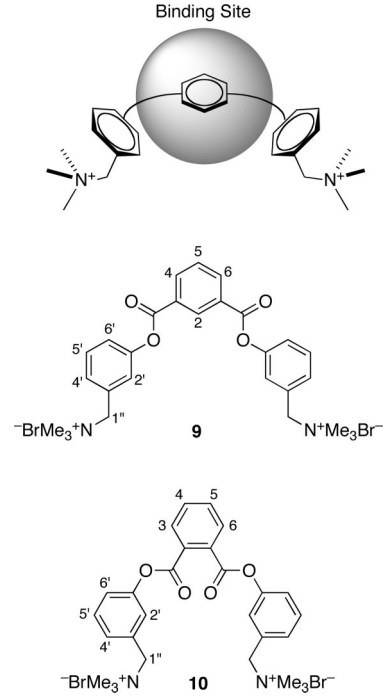
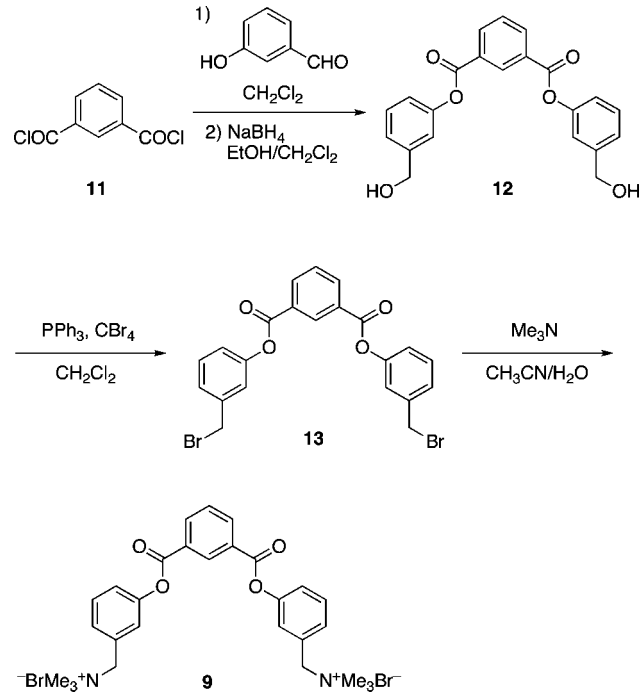


FIGURE 2. Concept of the water-soluble acyclic phane receptor and the synthesized receptor molecules (**9** and **10**).

SCHEME 1. Synthesis of the Meta-Substituted Receptor 9



Binding studies were carried out by ^{1}H NMR experiments in deuterium oxide. Although both the receptors (**9** and **10**) are quite soluble in water under neutral conditions, precipitation occurred upon catechin addition. However, the precipitates did not form under acidic conditions. This is most likely due to an increase in the hydrophilicity of the complexes by protonation of the hydroxy groups of the catechin molecules. Therefore, the binding abilities of the receptors were estimated in deuterium

(5) The following are studies on the acyclic phane receptors for catecholamines and quaternary ammonium cations, although these reports do not treat binding in aqueous solutions: (a) Campayo, L.; Calzado, F.; Cano, M. C.; Yunta, M. J. R.; Pardo, M.; Navarro, P.; Jimeno, M. L.; Gómez-Contreras, F.; Sanz, A. M. *Tetrahedron* **2005**, *61*, 11965–11975. (b) Molt, O.; Rübeling, D.; Schrader, T. *J. Am. Chem. Soc.* **2003**, *125*, 12086–12087. (c) Ito, K.; Miki, H.; Ohba, Y. *Yakugaku zasshi* **2002**, *122*, 413–417. (d) Roelens, S.; Torriti, R. *J. Am. Chem. Soc.* **1998**, *120*, 12443–12452. (e) Jeong, K.-S.; Hahn, K.-M.; Cho, Y. L. *Tetrahedron Lett.* **1998**, *39*, 3779–3782.

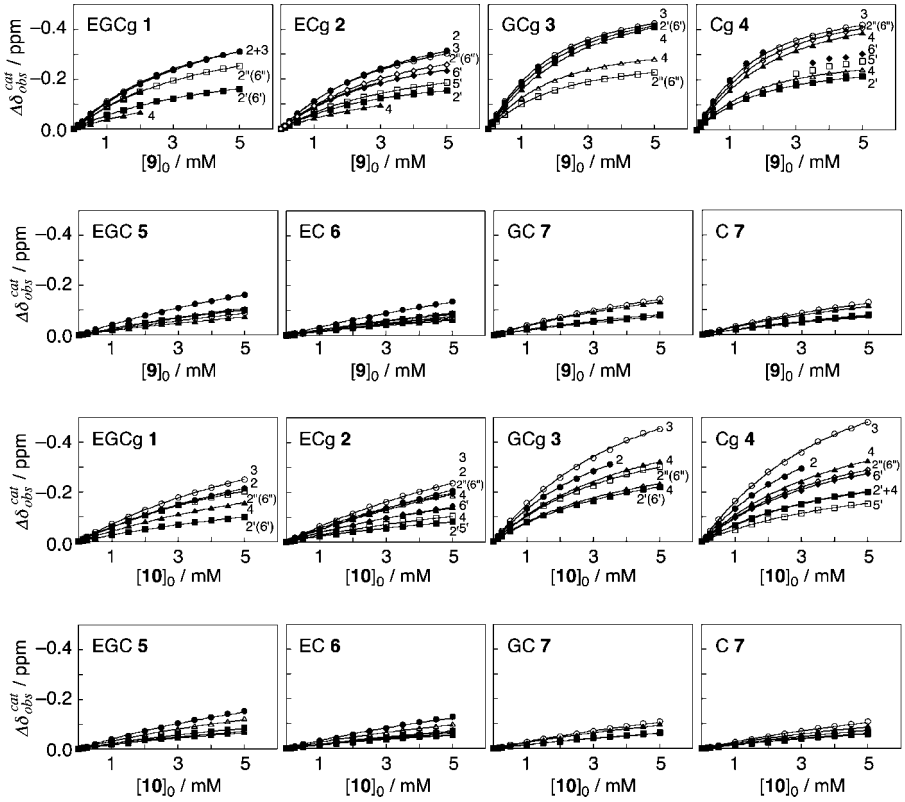


FIGURE 3. ^{1}H NMR titration curves between the receptors (**9** and **10**) and the catechins in D_2O at 300 K. $\Delta\delta_{obs}^{cat}$ is the difference between the observed ^{1}H NMR chemical shift of the catechins with and without the receptors. $[\mathbf{9}]_0$ and $[\mathbf{10}]_0$ are the total concentration of the receptors **9** and **10**, respectively. The numbers in the graphs identify the protons of the gallate-type catechins according to their attached carbon number (the corresponding numbers are not shown in the graphs for the nongallate-type catechins). Some data points are not plotted in the graphs because their ^{1}H NMR signals were hidden under the residual proton signal of D_2O or overlapped the adjacent proton signals. The protons on the A-ring (C6-H and C8-H) were not detected due to the substitution of deuterium for them.

TABLE 1. Binding Constants (M^{-1}) of the Complex between the Meta-Substituted Receptor (9) and Catechins at 300 K in D_2O

catechin protons	EGCg **1**	ECg **2**	GCg **3**	Cg **4**	EGC **5**	EC **6**	GC **7**	C **8**	GA[b] **14**
C2-H	289 ± 6	337 ± 11	−[a]	−[a]	94 ± 9	74 ± 16	−[a]	−[a]	
C3-H	345 ± 8	394 ± 11	810 ± 13	930 ± 33	54 ± 9	43 ± 14	109 ± 6	109 ± 15	
C4-H	−[a]	−[a]	491 ± 12	580 ± 16	61 ± 5	63 ± 15	118 ± 6	113 ± 14	
C4-H	−[a]	−[a]	790 ± 15	824 ± 24	66 ± 4	72 ± 16	82 ± 6	93 ± 16	
C2′ + 6′-H	291 ± 13		666 ± 12		70 ± 4		99 ± 8		
C2′-H		418 ± 13		757 ± 24		68 ± 15		100 ± 15	
C5′-H		322 ± 9		−[a]		66 ± 15		99 ± 15	
C6′-H		349 ± 13		−[a]		27 ± 12		89 ± 16	
C2″ + 6″-H	315 ± 8	352 ± 8	734 ± 11	737 ± 22					
mean	310 ± 9	362 ± 11	698 ± 13	766 ± 24	69 ± 6	59 ± 15	102 ± 7	100 ± 15	47 ± 14[c]

[a] These binding constants could not be determined, because the ^{1}H NMR signals were hidden under the residual proton signal of D_2O or overlapped the adjacent proton signals. [b] GA: gallic acid. [c] This binding constant was determined from ^{1}H NMR chemical shift changes in the aromatic protons of **14**.

oxide buffered by 0.1 M DCl/KCl.[6] The concentration of the receptors was increased from 0.00 to 5.00 mM against a constant concentration of the catechin (1.00 mM). Figure 3 shows the chemical shift changes ($\Delta\delta_{obs}^{cat}$) in each proton of the catechins against the total concentration of the receptors (**9** and **10**). All the ^{1}H NMR signals of the catechins shifted upfield with increasing concentration of the receptors. To investigate the stoichiometric ratios of the complexes between the receptors and the catechins, Job's plot experiments were performed by using ^{1}H NMR chemical shift changes in the benzyl protons (C1″-H) of the receptors.[7] In every case, the resulting graphs showed a maximum at 0.5 mol fraction. Consequently, the stoichiometric ratios of the complexes are revealed to be 1:1. To determine the binding constants, the standard binding isotherm for the formation of a 1:1 complex was applied to the ^{1}H NMR titration plots.[8] Tables 1 and 2 list the binding constants of the receptors (**9** and **10**) for the catechins, respectively. These binding constants indicate that the meta-substituted receptor **9** has the highest binding ability for the 2,3-*trans*-gallate-type catechins (**3** and **4**). Although the ortho-substituted receptor **10**

(6) The 0.1 M DCl/KCl−D_2O buffer was prepared by diluting the solution of 0.2 M DCl−D_2O (4.20 mL) and 0.2 M KCl−D_2O (45.80 mL) to 100 mL with D_2O. A pH meter in the buffer solution at 22 °C measured a pH of 1.8.

(7) Connors, K. A. *Binding Constants*; Wiley-Interscience: New York, 1987; pp 24−28.

(8) Hirose, K. *J. Inclusion Phenom. Macrocyclic Chem.* **2001**, *39*, 193–209.

TABLE 2. Binding Constants (M^{-1}) of the Complex between the Ortho-Substituted Receptor (10) and Catechins at 300 K in D_2O

catechin protons	EGCg **1**	ECg **2**	GCg **3**	Cg **4**	EGC **5**	EC **6**	GC **7**	C **8**	GA[b] **14**
C2-H	108 ± 3	47 ± 8	–[a]	–[a]	109 ± 16	89 ± 17	–[a]	–[a]	
C3-H	137 ± 5	99 ± 7	265 ± 15	278 ± 10	110 ± 18	70 ± 15	86 ± 17	84 ± 18	
C4-H	109 ± 13	143 ± 14	271 ± 15	265 ± 10	107 ± 17	80 ± 15	88 ± 18	80 ± 15	
C4-H	129 ± 5	88 ± 10	290 ± 16	289 ± 11	106 ± 16	88 ± 17	72 ± 15	76 ± 16	
C2′ + 6′-H	103 ± 11		301 ± 18		108 ± 16		77 ± 15		
C2′-H		131 ± 16		276 ± 11		86 ± 17		69 ± 15	
C5′-H		106 ± 16		241 ± 13		82 ± 14		76 ± 16	
C6′-H		103 ± 16		307 ± 19		66 ± 16		74 ± 16	
C2″ +6″-H	154 ± 5	132 ± 7	304 ± 17	297 ± 11					
mean	123 ± 7	106 ± 12	286 ± 16	279 ± 12	108 ± 16	80 ± 16	81 ± 16	77 ± 16	56 ± 14[c]

[a] These binding constants could not be determined because the ^{1}H NMR signals were hidden under the residual proton signal of D_2O. [b] GA: gallic acid. [c] This binding constant was determined from ^{1}H NMR chemical shift changes in the aromatic protons of **14**.

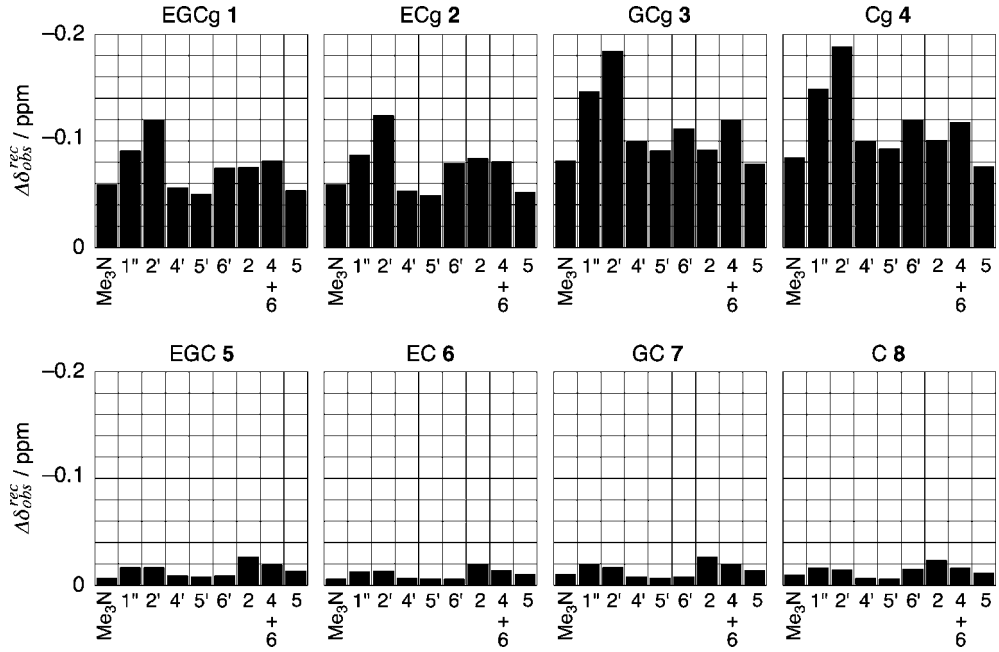


FIGURE 4. ^{1}H NMR chemical shift changes in the meta-substituted receptor **9** (1.00 mM) by addition of the catechins (1.00 mM) in D_2O at 300 K. $\Delta\delta_{obs}^{rec}$ is the difference between the observed ^{1}H NMR chemical shifts of the receptor with and without the catechins. The *x*-axis identifies the protons of **9** according to their attached carbon number.

also had a higher affinity for the 2,3-*trans*-gallate-type catechins than the other catechins, the binding constants of **10** for the 2,3-*trans*-gallate-type catechins were less than half of those of **9**. The binding abilities of **9** and **10** for the 2,3-*cis*-gallate-type catechins (**1** and **2**) and the nongallate-type catechins (**5**, **6**, **7**, and **8**) were low in both cases.

Furthermore, chemical shift changes in the protons of the receptors with the addition of the catechins were investigated (Figures 4 and 5). Concerning the meta-substituted receptor **9**, the profile of the chemical shift changes with the addition of EGCg **1** paralleled those with the addition of ECg **2** closely. The profile of the changes with the addition of GCg **3** paralleled those with the addition of Cg **4** closely. On the other hand, when nongallate-type catechins (**5**, **6**, **7**, and **8**) were added, all the chemical shift change profiles were similar and the shift changes were slight. These results suggest that complex structures are similar between **9**/**1** and **9**/**2**, between **9**/**3** and **9**/**4**, and between **9**/**5**, **9**/**6**, **9**/**7**, and **9**/**8**, respectively. For the ortho-substituted receptor **10**, the profiles of the chemical shift changes also had similar tendencies. From these results, it is concluded that the binding modes of both receptors, **9** and **10**, are grouped into three classes: (1) the mode for the 2,3-*cis*-gallate-type catechins (**1** and **2**); (2) the mode for the 2,3-*trans*-gallate-type catechins (**3** and **4**); and (3) the mode for the nongallate-type catechins (**5**, **6**, **7**, and **8**).

It is certain that the lower affinities of both receptors for the nongallate-type catechins are mainly caused by the decrease of hydrophobicity. In fact, the binding constants of the receptors (**9** and **10**) for gallic acid **14**, a monoaromatic compound, tended to be the lowest (Tables 1 and 2). The smaller binding constants of the ortho-substituted receptor **10** for the gallate-type catechins as compared with those of the meta-substituted receptor **9** might be explained from steric hindrance caused by the ester groups of **10**. It is presumed that the ester groups at the ortho-position cannot be coplanar with the central benzene ring by reason of steric and electrostatic repulsions. Therefore, as shown in Figure 6, the two ester groups or at least one of them protruding from the central benzene ring plane would weaken the interaction between the gallate-type catechin molecules and the central benzene ring by inhibiting the approach of the catechin molecules.

Although both the *cis*-catechins (**1** and **2**) and the *trans*-catechins (**3** and **4**) are of the gallate-type, the binding constants of the meta-substituted receptor **9** for the latter were larger. This

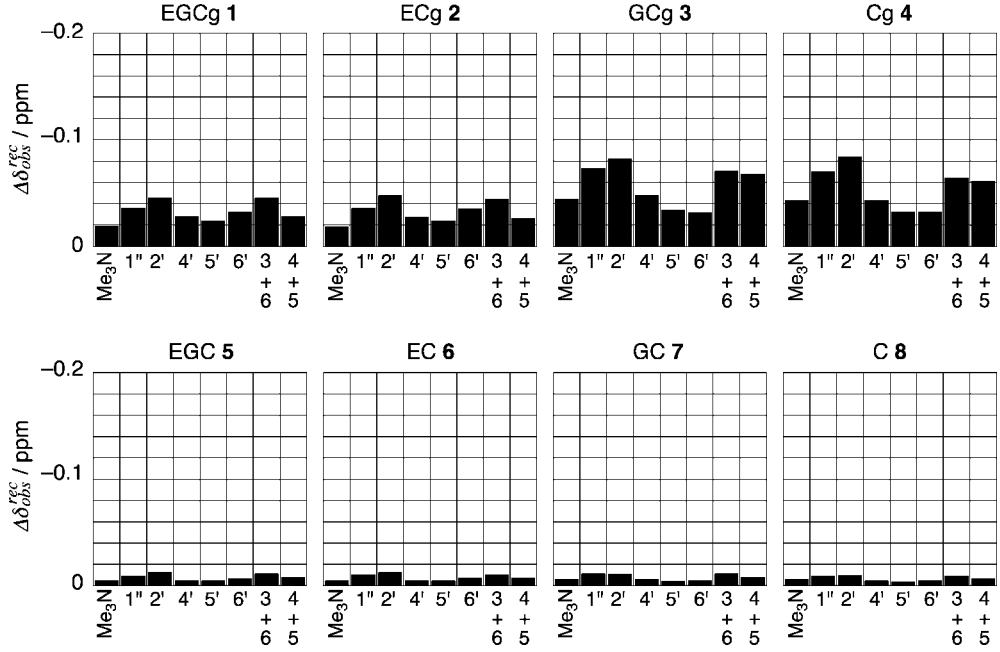


FIGURE 5. ^{1}H NMR chemical shift changes in the ortho-substituted receptor **10** (1.00 mM) by addition of the catechins (1.00 mM) in D_2O at 300 K. $\Delta\delta^{free}_{obs}$ is the difference between the observed ^{1}H NMR chemical shifts of the receptor with and without the catechins. The *x*-axis identifies the protons of **10** according to their attached carbon number.

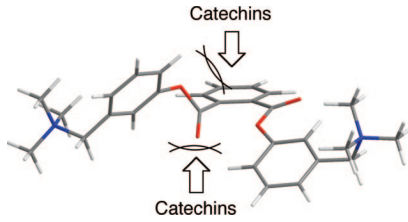


FIGURE 6. The stick model of the receptor **10**.

is most likely due to the conformational difference between the *trans*- and the *cis*-catechins. The 2,3-*cis*-gallate type catechins (**1** and **2**) would exist as a pseudoaxial galloyl group/pseudoequatorial B-ring conformer or a pseudoequatorial galloyl group/pseudoaxial B-ring conformer or both. On the other hand, the 2,3-*trans*-gallate-type catechins (**3** and **4**) would mainly exist as pseudoequatorial galloyl group/pseudoequatorial B-ring conformers. A NOESY spectrum in aqueous solution including **9** and GCg **3** showed intermolecular cross peaks only between the ammonium moieties of **9** and the B-ring/galloyl moieties of **3** (Figure 7a).[9] Consequently, **15** as illustrated typically in Figure 8 is proposed as the candidate of the major complex structure between **9** and **3**. This structure **15** seems to achieve efficient interaction between the hydrophobic space of **9** and the three aromatic rings of **3** with little strain. Moreover, the conformations of both **9** and the 2,3-*trans*-gallate-type catechins in this complex structure might be close to the stable conformations of each individual molecule under free conditions. In this case, it is presumed that the formation of **15** is favorable from

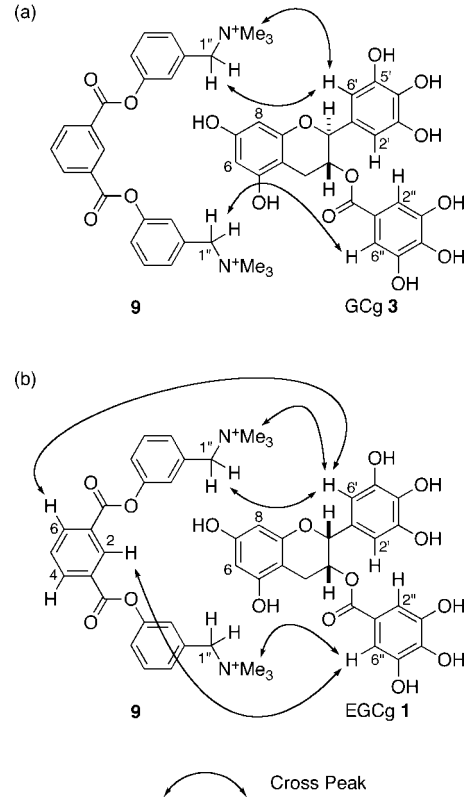


FIGURE 7. The intermolecular cross peaks in the NOESY spectra.

both the interaction energy and the deformation energy for both molecules (**9** and **3**). Although other complex structures would also exist because of the flexibility of the acyclic receptor, there is a possibility that the **15**-type complex is more stable due to conformational matching between the receptor and the catechin molecules. On the other hand, a NOESY spectrum for the aqueous solution including **9** and EGCg **1** showed intermolecular cross peaks between C4(6)-H of **9** and C2′(6′)-H of **1** and

(9) Intermolecular cross peaks between the protons on the central ring of **9** and the protons on the A-ring of **3** are not observed. These peaks are not detected due to the substitution of deuterium for C6-H and C8-H even though the distance between these protons is small. However, there is little possibility that the cross peaks between the ammonium moieties and the B-ring/galloyl moieties of **3** result from the CH/π (or cation/π) interaction, because it is presumed that this interaction is extremely weak in polar solvents such as water. Moreover, if the CH/π (or cation/π) interaction is a major binding force, the binding constant of EGCg **1** for **9** should be a little larger than that of the 2,3-*trans*-gallate-type catechins (see ref 1).

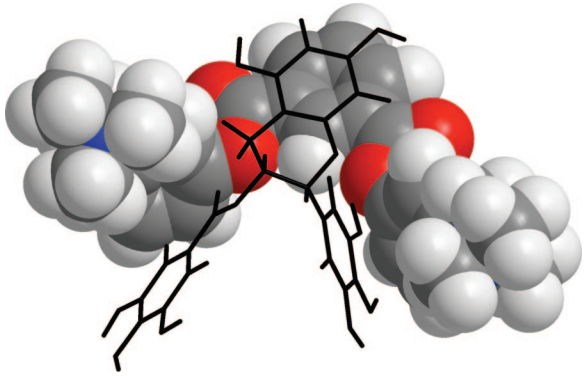


FIGURE 8. The proposed complex structure **15** formed by the meta-substituted receptor **9** (space filling model) and GCg **3** (stick model).

between C2-H of **9** and C2″(6″)-H of **1** in addition to the cross peaks between the ammonium moieties of **9** and the B-ring/galloyl moieties of **1** (Figure 7b). These results suggest that plural complex structures with similar energies exist between **9** and **1**. From the binding studies and the NOESY experiments, it is probable that the conformational matching effect such as in the case of the 2,3-*trans*-gallate-type catechins is not gained in the complex between **9** and the 2,3-*cis*-gallate-type catechins because of the conformational difference between the 2,3-*cis*-gallate-types and the 2,3-*trans*-gallate-types. Similar reasons might also account for the larger binding constants of **10** for the 2,3-*trans*-gallate-type catechins compared to those for the 2,3-*cis*-gallate type catechins.

In this study, we synthesized two water-soluble acyclic phane receptors for gallate-type catechins and evaluated their binding abilities in water. It was found that the meta-substituted receptor **9** showed the best affinity for the gallate-type catechins, the 2,3-*trans*-types (**3** and **4**) in particular. The receptor **9** is certain to achieve recognition by the difference in both the hydrophobicity and the conformation of the catechin molecules. It is very interesting that the acyclic phane receptor **9**, a fairly simple molecule, can distinguish differences in the structures of the catechin analogues. It is expected that the chemical structure of **9** can be applied to chemical sensor systems.

Experimental Section

Bis[3′-(hydroxymethyl)phenyl] Isophthalate (12). Pyridine (2.34 mL, 28.9 mmol) and isophthaloyl chloride **11** (1.95 g, 9.62 mmol) were added to a solution of 3-hydroxybenzaldehyde (2.30 g, 18.8 mmol) in CH_2Cl_2 (200 mL) at 0 °C. The solution was stirred at 0 °C for 30 min, then 25 °C for 2 h. The reaction mixture was poured into a flask with ice and extracted with ethyl acetate (EtOAc). The organic phase was washed with 1 M aq HCl, satd aq sodium hydrogencarbonate ($NaHCO_3$), and brine, then dried over anhydrous magnesium sulfate ($MgSO_4$). The dried solution was filtered and the filtrate was concentrated in vacuo. The residue was solved in CH_2Cl_2. Hexane was added to the solution to form a white precipitate, which was isolated by a Kiriyama funnel.

Sodium borohydride ($NaBH_4$) (0.241 g, 6.05 mmol, purity 95%) was added to the solution of the precipitate in ethanol (120 mL) and CH_2Cl_2 (50 mL) at 0 °C. The solution was stirred at 0 °C for 1.5 h. The reaction was quenched by adding 1 M aq HCl dropwise. The resulting mixture was diluted with EtOAc, washed with 1 M aq HCl, satd aq $NaHCO_3$, and brine, then dried over anhydrous $MgSO_4$. The dried solution was filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2, 1:1 to 2:3 hexane−EtOAc) to give diol **12** (1.31 g, 36% for 2 steps) as a white solid: mp 90 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.01 (1H, t, J = 1.9 Hz), 8.47 (2H, dd, J = 1.9, 8.0 Hz), 7.70 (1H, t, J = 8.0 Hz), 7.45 (2H, t, J = 8.0 Hz), 7.30 (2H, br d, J = 8.0 Hz), 7.29 (2H, br s), 7.18 (2H, br dd, J = 2.5, 8.0 Hz), 4.76 (4H, d, J = 6.1 Hz), and 1.76 (2H, t, J = 6.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.3 (C), 150.9 (C), 142.9 (C), 135.0 (CH), 131.7 (CH), 130.3 (CH), 129.7 (CH), 129.1 (C), 124.4 (CH), 120.7 (CH), 120.0 (CH), and 64.7 (CH_2); IR (KBr) 3317, 3088, 3063, 2925, 2880, 1734, 1607, 1590, 1490, and 1448 cm^{-1}; HR-EI-MS, calcd for $C_{22}H_{18}O_6$ (M^+) 378.1103, found 378.1091.

Bis[3′-(bromomethyl)phenyl] Isophthalate (13). Carbon tetrabromide (CBr_4) (3.08 g, 9.30 mmol) and triphenylphosphine (Ph_3P) (1.95 g, 7.44 mmol) were added to a solution of diol **12** (1.17 g, 3.10 mmol) in CH_2Cl_2 (60 mL) at 25 °C. The solution was stirred at 25 °C for 15 min, and then CBr_4 (0.308 g, 0.929 mmol) and Ph_3P (0.195 g, 0.743 mmol) were added. The solution was stirred for 30 min then methanol (6.3 mL) was added and the solution was stirred an additional 10 min before the solvent was removed in vacuo. The residue was purified by flash column chromatography (SiO_2, 10:1 to 4:1 hexane−EtOAc) to give dibromide **13** (1.34 g, 86%) as a white solid: mp 110 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.01 (1H, dt, J = 0.6, 1.8 Hz), 8.47 (2H, dd, J = 1.8, 7.9 Hz), 7.71 (1H, dt, J = 0.6, 7.9 Hz), 7.43 (2H, t, J = 8.3 Hz), 7.33 (2H, ddd, J = 1.2, 1.6, 8.3 Hz), 7.32 (2H, dd, J = 1.6, 2.1 Hz), 7.20 (2H, ddd, J = 1.2, 2.1, 8.3 Hz), and 4.52 (4H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.0 (C), 150.8 (C), 139.5 (C), 135.1 (CH), 131.8 (CH), 130.2 (C), 129.9 (CH), 129.2 (CH), 126.7 (CH), 122.3 (CH), 121.7 (CH), and 32.4 (CH_2); IR (KBr) 3078, 3037, 1744, 1609, 1589, 1483, 1450, and 1436 cm^{-1}; HR-EI-MS, calcd for $C_{22}H_{16}Br_2O_4$ (M^+) 501.9415, found 501.9431.

Bis[3′-(trimethylammoniomethyl)phenyl] Isophthalate Dibromide (9). Trimethylamine (30% in water) (5 mL) was added to a solution of dibromide **13** (0.388 g, 0.770 mmol) in acetonitrile (20 mL) at 0 °C. The solution was stirred for 30 min, and then trimethylamine (30% in water) (5 mL) was added. The solution was stirred at 0 °C an additional 30 min before the solvent was removed in vacuo. The residue was recrystallized twice from methanol−EtOAc to give quaternary ammonium salt **9** (0.220 g, 46%) as a white solid: mp 238−239 °C dec; ^{1}H NMR (500 MHz, D_2O) δ 8.80 (1H, t, J = 1.5 Hz, C2-*H*), 8.35 (2H, dd, J = 1.5, 8.0 Hz, C4(6)-*H*), 7.64 (1H, t, J = 8.0 Hz, C5-*H*), 7.50 (2H, t, J = 8.3 Hz, C5′-*H*), 7.37 (2H, br d, J = 8.3 Hz, C4′-*H*), 7.34 (2H, br d, J = 8.3 Hz, C6′-*H*), 7.33 (2H, br s, C2′-*H*), 4.38 (4H, s, C1”-*H*), and 2.95 (18H, s, N-*Me*); ^{13}C NMR (125 MHz, D_2O) δ 166.5 (C), 150.6 (C), 135.6 (CH), 131.6 (CH), 131.2 (CH), 130.8 (CH), 129.8 (CH), 129.4 (C), 129.2 (C), 126.0 (CH), 124.3 (CH), 68.9 (CH_2), and 52.6 (CH_3); IR (KBr) 3022, 2961, 1740, 1609, 1588, 1490, and 1449 cm^{-1}; HR-FAB-MS, calcd for $C_{28}H_{34}BrN_2O_4$ (M^+ − Br) 541.1702, found 541.1703.

Bis[3′-(hydroxymethyl)phenyl] Phthalate (16). Pyridine (2.35 mL, 29.1 mmol) and phthaloyl chloride (1.40 mL, 9.70 mmol) were added to a solution of 3-hydroxybenzaldehyde (2.31 g, 18.9 mmol) in CH_2Cl_2 (150 mL) at 0 °C. The solution was stirred at 0 °C for 1 h, then 25 °C for 3 h. The reaction mixture was poured into a flask with ice, then extracted with EtOAc. The organic phase was washed with 1 M aq HCl, satd aq $NaHCO_3$, and brine, then dried over anhydrous $MgSO_4$. The dried solution was filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 5:1 to 2:1 hexane−EtOAc) to give bisester (2.76 g) with a byproduct.

$NaBH_4$ (0.294 g, 7.37 mmol, purity 95%) was added to the solution of the bisester in ethanol (70 mL) and THF (30 mL) at 0 °C. The solution was stirred at 0 °C for 30 min. The reaction was quenched by adding 1 M aq HCl dropwise. The resulting mixture was diluted with EtOAc, washed with 1 M aq HCl, satd aq $NaHCO_3$ and brine, then dried over anhydrous $MgSO_4$. The dried solution was filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2, 1:1 to 2:3

hexane−EtOAc) to give diol **16** (2.50 g, 90%) as a white solid: mp 75 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (2H, AA′BB′ system), 7.71 (2H, AA′BB′ system), 7.39 (2H, t, J = 7.6 Hz), 7.24 (2H, br s), 7.23 (2H, br d, J = 7.6 Hz), 7.16 (2H, ddd, J = 0.6, 2.5, 7.6 Hz), 4.61 (4H, d, J = 5.8 Hz), and 2.42 (2H, t, J = 5.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0 (C), 150.9 (C), 142.9 (C), 131.8 (CH), 131.6 (C), 129.6 (CH), 129.5 (CH), 124.6 (CH), 120.6 (CH), 120.0 (CH), and 64.5 (CH_2); IR (KBr) 3267, 3068, 2925, 2875, 1739, 1611, 1590, 1577, 1488, and 1444 cm^{-1}; HR-EI-MS, calcd for $C_{22}H_{18}O_6$ (M^+) 378.1103, found 378.1093.

Bis[3′-(bromomethyl)phenyl] Phthalate (17). CBr_4 (1.17 g, 3.54 mmol) and Ph_3P (0.742 g, 2.83 mmol) were added to a solution of diol **16** (0.446 g, 1.18 mmol) in CH_2Cl_2 (24 mL) at 25 °C. The solution was stirred at 25 °C for 20 min then methanol (2.0 mL) was added. The solution was stirred an additional 10 min before the solvent was removed in vacuo. The residue was purified by flash column chromatography (SiO_2, 10:1 to 1:1 hexane−EtOAc) to give dibromide **17** (0.519 g, 87%) as a white solid: mp 83 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (2H, AA′BB′ system), 7.72 (2H, AA′BB′ system), 7.38 (2H, t, J = 7.9 Hz), 7.30 (2H, ddd, J = 1.3, 2.2, 7.9 Hz), 7.26 (2H, dd, J = 0.9, 1.3 Hz), 7.18 (2H, ddd, J = 0.9, 2.2, 7.9 Hz), and 4.46 (4H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6 (C), 150.8 (C), 139.5 (C), 131.9 (CH), 131.5 (C), 129.9 (CH), 129.6 (CH), 126.8 (CH), 122.1 (CH), 121.6 (CH), and 32.4 (CH_2); IR (KBr) 3073, 3027, 1749, 1485, and 1446 cm^{-1}; HR-FAB-MS, calcd for $C_{22}H_{17}Br_2O_4$ (M^+ + H) 502.9494, found 502.9480.

Bis[3′-(trimethylammoniomethyl)phenyl] Phthalate Dibromide (10). Trimethylamine (30% in water) (17 mL) was added to a solution of dibromide **17** (0.642 g, 1.27 mmol) in acetonitrile (34 mL) at 0 °C. The solution was stirred at 0 °C for 30 min and the solvent was removed in vacuo. The residue was recrystallized from methanol−acetone−hexane to give quaternary ammonium salt **10** (0.242 g from first recrystallization, 31%) as a white solid: mp 232−233 °C dec; ^{1}H NMR (500 MHz, D_2O) δ 7.95 (2H, AA′BB′ system, C3(6)-*H*), 7.70 (2H, AA′BB′ system, C4(5)-*H*), 7.45 (2H, dd, J = 7.8, 8.9 Hz, C5′-*H*), 7.36 (2H, br d, J = 7.8 Hz, C4′-*H*), 7.29−7.27 (2H, m, C6′-*H*), 7.28 (2H, m, C2′-*H*), 4.33 (4H, s, C1″-*H*), and 2.90 (18H, s, N-*Me*); ^{13}C NMR (125 MHz, D_2O) δ 168.3 (C), 150.4 (C), 133.2 (CH), 131.4 (CH), 130.9 (CH), 130.1 (C), 129.9 (CH), 129.3 (C), 125.7 (CH), 124.0 (CH), 68.8 (CH_2), and 52.5 (CH_3); IR (KBr) 3007, 2961, 1738, 1586, 1489, and 1449 cm^{-1}; HR-FAB-MS, calcd for $C_{28}H_{34}BrN_2O_4$ (M^+ − Br) 541.1702, found 541.1702.

Acknowledgment. This work was financially supported by the NIVTS priority research program.

Supporting Information Available: General experimental methods and the following experimental procedures: Job's plots, ^{1}H NMR titrations, NOESY experiments, and chemical shift changes in the protons of **9** and **10** with the addition of the catechins; Job's plot curves (Figure S1); ^{1}H and ^{13}C NMR spectra for **9**, **10**, **12**, **13**, **16**, and **17**; NOESY spectrum in aqueous solutions including **9** and **3**; and NOESY spectrum in aqueous solutions including **9** and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO800406E