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Molecular Receptor for Binding Quaternary Ammonium Salts and a Large Anion Effect on the Complexation

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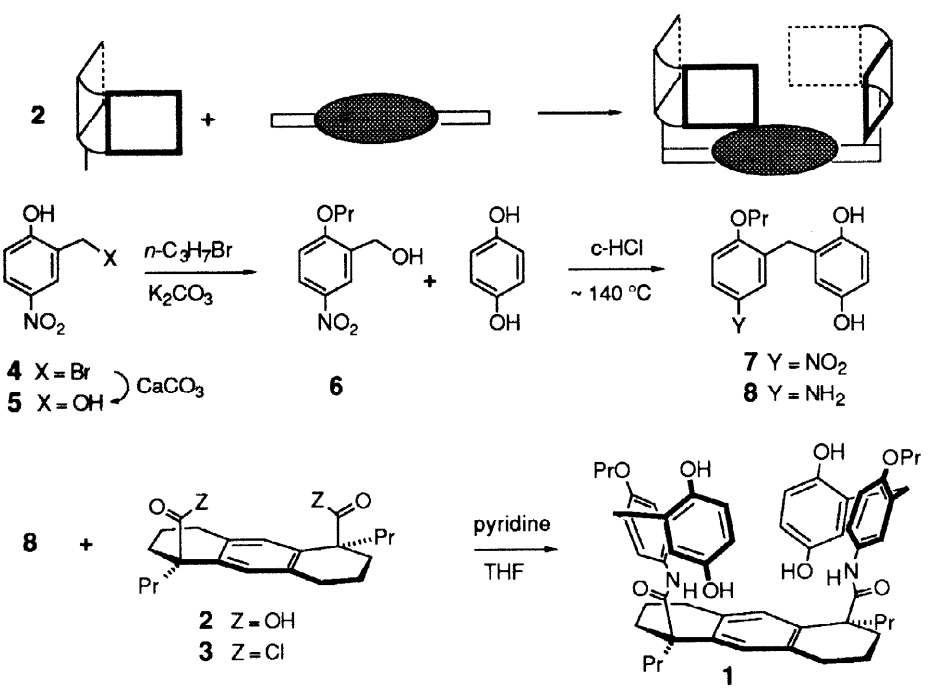
Abstract: An acyclic receptor **1** with a binding cavity surrounded by electron-rich aryl surfaces has been synthesized for binding quaternary ammonium salts through cation-π interactions. The association constants of the receptor **1** with salts in $CDCl_3$ depend on the anions due to the hydrogen bonds between the exchangeable protons in the receptor **1** and anions.

The cation-π interactions are now known to play the important roles in the stabilization of the complexes between quaternary ammoniums and biological or synthetic receptors that contain electron-rich aromatic surfaces.[1] The synthetic receptors for binding quaternary ammoniums studied so far are mostly cyclic molecules such as cyclophanes,[2] crytophanes,[3] and calixarenes.[4] We report here the synthesis and binding property of a new acyclic receptor having a large cavity surrounded by electron-rich aryl surfaces. Our approach to design the acyclic receptor is schematically shown in Scheme 1, in which two concave subunits are diagonally connected to a highly rigid building block, *cis*-1,2,3,4,5,6,7,8-octahydroanthracene-1,5-dipropyl-1,5-dicarboxylic acid (**2**). A diphenylmethane derivative with electron donor substituents is chosen for the construction of aryl surface walls of the receptor **1**.

Scheme 1



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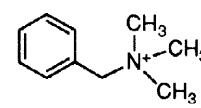
The synthesis of the receptor **1** is outlined in Scheme 1. We previously described the synthesis of the dicarboxylic acid **2** and modification to the dicarboxylate receptors.[5] 2-Hydroxy-5-nitrobenzyl alcohol (**5**) obtained from the corresponding bromide **4**,[6] was treated 1-bromopropane/K_2CO_3 in acetone to give the compound **6** in 69% yield. Introduction of the propyl groups greatly increases solubility (~ 10 mM in $CDCl_3$) of the receptor **1** to investigate conveniently the binding properties. A mixture of **6** and excess (10 equiv) hydroquinone in aqueous c-HCl was heated at ~ 140 °C for 17 h to afford the diphenylmethane derivative **7** in 71% yield.[7] After reduction of **7** with H_2/Pd-C in methanol, coupling of the resulting amine **8** with **3** gave the desired receptor **1** in 33% yield.[8]

The binding affinities of the receptor **1** to $CDCl_3$-soluble quaternary ammonium salts were determined by nonlinear least-squares fitting method of the saturation curves obtained from ^1H NMR titrations. During the titrations by varying concentrations of **1** (0 to 5.33 mM) and guest (2.00 to 0.67 mM in $CDCl_3$), the signals for the guest N^+CH_n protons are gradually upfield-shifted. The observed maximum chemical shifts as well as the association constants (K_a, M^{-1}) are summarized in Table 1.

Table 1. Association constants (Ka, M^{-1}) and upfield shifts on the complexations of receptor **1** and guests in $CDCl_3$ at 296 ± 0.5 K.

entry	guest	obsd $\Delta\delta_{max}$ (N^+CH_3)[a]	obsd $\Delta\delta_{max}$ (N^+CH_2)[a]	K_a (M^{-1})
1	**9** Cl^-	0.96	1.18	1070 ± 50
2	**9** Br^-	0.81	1.00	340 ± 10
3	**9** I^-	0.66	0.69	56 ± 1
4	**10** I^-	0.65	0.64	135 ± 1
5	**11** I-	0.61	0.61	129 ± 2
6	**12** I^-	0.72	-	340
7	**13**	no change	-	no binding
8[b]	**9** Cl^-	0.15	0.19	27 ± 2
9[b]	**9** Br^-	0.18	0.22	31 ± 1
10[b]	**9** I^-	0.24	0.30	40 ± 1



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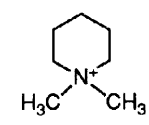

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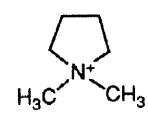

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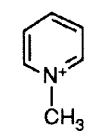

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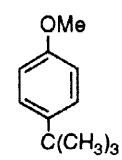

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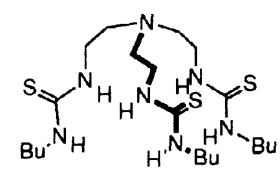

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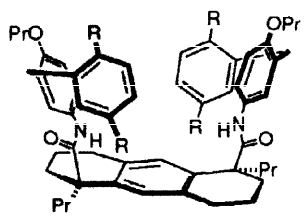
[a]. Obsd $\Delta\delta_{max}$ (observed maximum upfield shift of the guest signal) = δ_{free} (chemical shift of free guest) - δ_{max} (chemical shift at the end of titration). [b]. The ^1H NMR titrations were performed in presence of the tris(thiourea) **14** (10 mM).

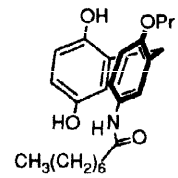
The magnitudes of the association constants in Table 1 were comparable to or greater than the reported values [2c,4c,e,i] between cyclic receptors and quaternary ammonium ions under the same condition. It is also worthwhile to mention that no complexation occurs between the neutral guest **13** and the receptor **1** (entry 7). Furthermore, the association constants (K_a) between the receptor **1** and benzyltrimethylammonium (**9**) chloride, bromide, and iodide (entry 1-3) are 1,070, 340, and 56 M^{-1}, respectively. These results are quite surprising

because quaternary ammonium chloride among them exists in the tightest ion pair in a nonpolar solvent, $CDCl_3$, and thus expected to give the lowest association constant.[4e-f] Another important observation is that the ^1H NMR signals for exchangeable protons (amide NH and phenolic OHs) of **1** are considerably downfield-shifted upon addition of quaternary ammonium salts, indicating hydrogen bonding occurs between exchangeable protons and halides. More specifically, addition of n-$Bu_4N^+X^-$ (~ 15 equiv) to 0.5 mM solution of **1** in $CDCl_3$ caused the following downfield shifts ($\Delta\delta$, ppm): NH (0.56), two OHs (0.64, 2.91) for X=Cl; NH (0.31), two OHs (0.37, 1.54) for X= Br; NH (0.08), two OHs (0.11, 0.35) for X = I. The trend of downfield shifts is consistent with hydrogen-bonding acceptor abilities of halides ($Cl^- > Br^- > I^-$).[9]

In order to further investigate anion effects on the binding events, tris(thiourea) **14** as an anion sequestrator[10] was prepared by the reaction of tris(2-aminoethyl)amine with excess butyl isothiocyanate. Titrations in the presence of excess **14** (10 mM)[11] gave a similar association constants (entry 8-10, K_a 27 ~ 40 M^{-1}) regardless of the kind of anions, but the magnitudes were significantly decreased in the cases of **9**·Cl^- and **9**·Br^-. In addition, we prepared analogous receptors **15**, **16** and **17**, in which the OH group in **1** was replaced by H, Me, or OMe, respectively. When the receptors **15**, **16** and **17** were added to the solution of **9**·X^-, the chemical shift changes were very small ($\Delta\delta_{max}$ (obsd) < 0.1 ppm), and thus the reliable binding constants could not be obtained. Based on the observations described so far, the large anion effects on binding in our system could be explained by hydrogen bonding between exchangeable protons and anions that may increase the electron density in the aryl surface walls and thus provide the stronger cation-π interactions. This explanation is consistent with the theoretical calculations by Dougherty *et. al.* [12] stating that the cation-π interaction between Na^+ and phenol was considerably enhanced when the OH of phenol was hydrogen-bonded with formamide.



15 R = H
16 R = Me
17 R = OMe



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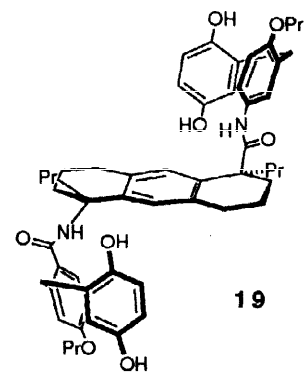

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Three different experiments were performed to obtain the structural informations of the complexes between receptor **1** and guests. First, Job's plots[13] confirm that all of the guests studied here form 1:1 complexes with **1**. Second, 2D ROESY experiments using a 1:1 molar mixture of the receptor **1** and **10**·Cl^- showed intermolecular cross peaks between guest $N^+(CH_3)_3$ and all of aryl wall hydrogens in **1**, indicating that $N^+(CH_3)_3$ hydrogens of the guest **9** are closely contacted on the aryl surfaces of the receptor **1**. Finally, the association constants of **9**·Cl^- with two reference compounds, the wall-forming diphenylmethane derivative **18** and the *trans* isomer **19**[14], are 92± 7 M^{-1} and 220 ± 10 M^{-1}, respectively, which are much smaller than that (1070 ± 50 M^{-1}) with receptor **1** under same conditions. These three observations clearly suggest that two diphenylmethane units in **1** simultaneously participated in binding and the ammonium cations located in a cavity surrounded by aryl surfaces of the receptor **1**.

In conclusion, a new acyclic receptor **1**, like cyclic analogues such as calixarenes, binds efficiently quaternary ammonium salts in $CDCl_3$. The binding affinities depend on the anions possibly due to hydrogen bonds between the receptor **1** and anions.

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8. Yield was not optimized. Physical properties of **1**: Mp 124-126 °C; ^{1}H NMR (250 MHz, $CDCl_3$), δ 7.36 (dd, 2H, J = 8.8, 2.5 Hz), 7.29 (s, 2H), 7.14 (s, 2H), 6.86 (d, 2H, J = 2.5 Hz), 6.74 (d, 2H, J = 8.8 Hz), 6.57 (d, 2H, J = 8.6 Hz), 6.54 (s, 2H), 6.45 (dd, 2H, J = 8.6, 2.9 Hz), 6.34 (d, 2H, J = 2.9 Hz), 5.90 (s, 2H), 3.96 (t, 4H, J = 6.7 Hz), 3.63 (d, 2H, J = 14.3 Hz), 3.37 (d, 2H, J = 14.3 Hz), 2.74 (m, 4H), 2.42 (m, 2H), 2.01-2.16 (m, 4H), 1.73-1.94 (m, 10H), 1.16-1.48 (m, 4H), 1.05 (t, 6H, J = 7.4 Hz), 0.95 (t, 6H, J = 7.2 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$), δ 176.8, 152.6, 150.2, 148.1, 137.5, 137.1, 131.9, 129.8, 129.7, 127.8, 123.7, 120.9, 117.6, 117.5, 115.5, 113.0, 71.5, 52.1, 41.4, 32.9, 31.0, 30.6, 23.0, 20.9, 18.7, 15.4, 11.1; Anal. Calcd for $C_{54}H_{64}N_2O_8$: C, 74.63; H, 7.42; N, 3.22. Found: C, 74.60; H, 7.50; N, 3.21.
9. The infrared spectrum of the receptor **1** in the presence of excess (~ 5 equiv) $(n\text{-Bu})_4N^+Cl^-$ or $(n\text{-Bu})_4N^+Br^-$ show a new broad band near 3200 cm^{-1} corresponding to the hydrogen-bonded NH groups.
10. For other anion-binding receptors, see: (a) Valiyayeettil, S; Engbersen, J. F. J.; Verboom, W.; Reinhoudt, D. N. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 900-901. (b) Beer, P. D. *J. Chem. Soc., Chem. Comm.* **1996**, 689-696.
11. Association constants of the tris(thiourea) **14** with Cl^-, Br^- and I^- are >5.0 x 10^4, 3.6 x 10^3, and 56 M^{-1}, respectively, in 20% DMSO-d_6 in $CDCl_3$ at 296 K. Most of Cl^- and Br^- might therefore exist as the complexes with **14** under the titration conditions, that is, 10 mM of **14** and 0.67-2.00 mM of $9{\cdot}X^{-1}$ in $CDCl_3$.
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14. The *trans* receptor **19** was prepared by coupling **8** with the *trans* isomer of **3** (see ref. 5).