Synthesis and Anion Recognition of Cholic Acid-based Tripodal Receptor: A Chloride Selective Anion Receptor

Ki Soo Kim, Nam Ju Cho, and Hong-Seok Kim*

*Department of Applied Chemistry, Kyungpook National University, Daegu 702-701, Korea. *E-mail: kimhs@knu.ac.kr*
Received March 23, 2006

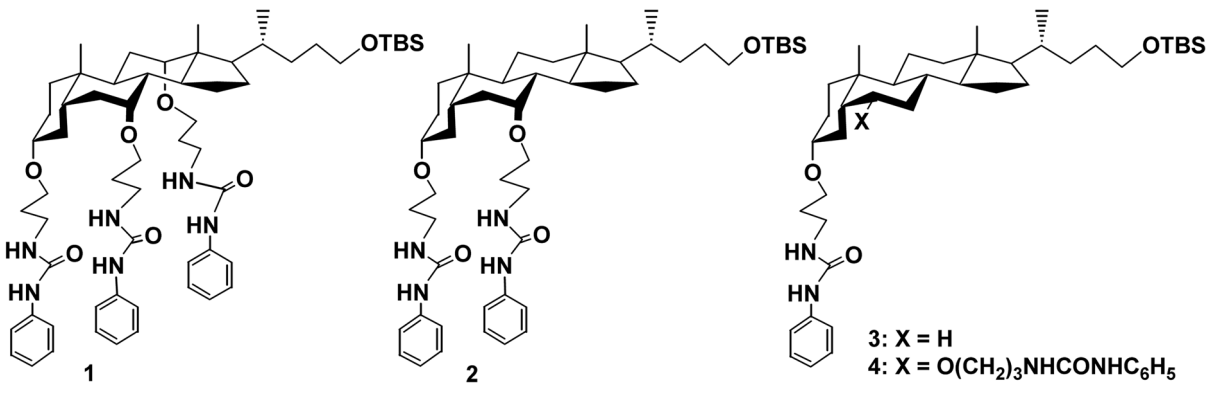
Synthesis of cholic acid-based tripodal receptor (**1**) and its high chloride ion affinity in comparison with that of chenodeoxycholic acid (**2**) and lithocholic acid-based receptor (**3**) was achieved. Anion binding affinities of the receptors were evaluated by ^{1}H NMR and ITC titrations. Tripodal receptor **1** showed a selective affinity for Cl^- over Br^-, I^-, $H_2PO_4^-$, and $CH_3CO_2^-$. The selectivity of **1** for Cl^- is about 3 times that of Br^-, and 17 times that for $H_2PO_4^-$.

Key Words : Cholic acid, Urea, Hydrogen bonds, Anion recognition, Chloride ion

Introduction

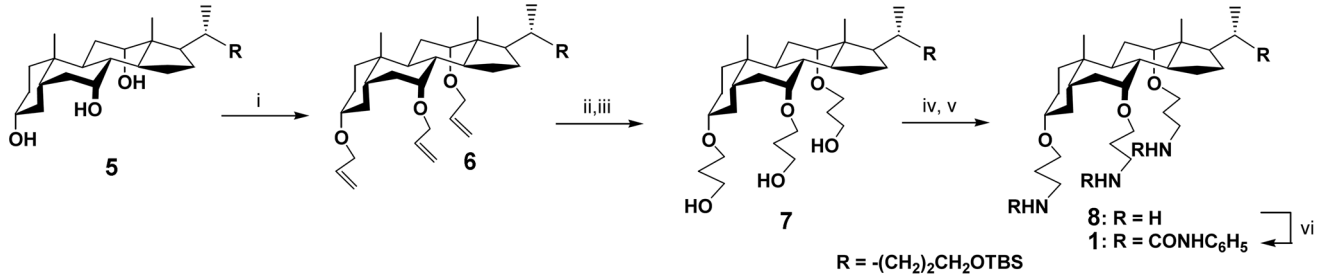
Selective recognition of anions via artificial receptors has attracted increasing interest in recent years because of their significant importance and potential applications in the biological, environmental, and supramolecualr chemistry.[1] Chloride ions are among the main ions in biological fluids and determination of their concentration is import in clinical analysis.[2] Chloride transporters across vesicle and cell membranes have potential as treatments for cystic fibrosis.[3] Despite this importance, there have been few investigations of chloride selective ionophore[4] or of chloride transport by synthetic receptors.[5] Direct detection of specific anions in aqueous systems is essential for the development of ion sensors for applications in clinical and environmental analyses. Steroid is one of the largest rigid system and chiral ubiquitous natural material. Based on these preorganized structural characteristics, cholesterol and bile acid derivatives have been used as building blocks for extended, well defined molecular architectures and a scaffold of synthetic receptors, and have shown selectivity towards cations, anions, and organic molecules.[6,7] Davis and co-workers synthesized tripodal anionophores by attaching three NH-containing groups to cholic acid at 3, 7, and 12 positions and evaluated their anion affinity.[8] They found that tripodal anionophores derived from cholic acid forms remarkably strong complexes with fluoride and chloride through cooperative hydrogen bonds in an organic solution. This discovery has led to the incorporation of hydrogen bond donor unit in steroid receptors.[9]

To enhance the anion affinity of this motif, we synthesized chenodeoxycholic acid and hyodeoxycholic acid-based molecular tweezer receptors containing two urea units in a steroid skeleton. Chenodeoxycholic acid-based molecular tweezer receptor **2** was found to bind with Cl^- (Ka = 2,750 M^{-1}) in a $CDCl_3$.[10] Hyodeoxycholic acid-based molecular tweezer receptor **4** showed approximately 170 times higher affinity towards F^- over Cl^-. Receptor **4** exhibited two kinds of binding modes with F^-. It initially formed a 1 : 1 complex ($K_1 = 2.99 \times 10^4$ M^{-1}) and became 1 : 2 complex ($K_2 = 1.37 \times 10^6$ M^{-1}) with increasing concentration of F^- in a DMSO solution.[11] It is well known that receptors bearing two urea moieties at suitable positions binds anion through hydrogen bonds.[12] Therefore, the size of the anion and distance between two urea pendants of steroid receptor is an important factor to determine the binding affinity. Results from molecular tweezer receptors **2** and **4** provided a clear potential for improvement of binding affinity; further introduction of hydrogen bond donor unit could improve affinity. As shown in Figure 1, we designed a tripodal receptor based on cholic



1 2

Figure 1



Scheme 1. i) NaH, CH_2=$CHCH_2Br$, THF; ii) 9-BBN, THF; iii) $NaOH/H_2O_2$; iv) DEAD, PPh_3, phthalimide, THF; v) $H_2NNH_2 \cdot H_2O$, EtOH; vi) C_6H_5NCO, $CHCl_3$.

acid and evaluated its anion binding affinity with two other receptors bearing different number of urea pendants.

In this paper, we report that the synthesis of cholic acid-based tripodal receptor (**1**) and its high chloride ion affinity in comparison with that of chenodeoxycholic acid (**2**) and lithocholic acid-based receptor (**3**).

Results and Discussion

The synthesis of the 3α,7α,12α-tris(ureidopropanoxy)-5β-cholane-based tripodal receptor **1** is described in Scheme 1. Commercially available cholic acid was easily converted into the corresponding tris(allyl)ether **6** by allylation of trihydroxy compound **5** with allyl bromide in the presence of NaH. 3,7,12-Tris(allyloxy)-5β-cholane was transformed to the amine by two sequential steps: hydroboration of double bond in **6** with 9-BBN followed by basic work-up yielded tris(3'-hydroxypropanoxy)ether **7**, and subsequent transformation of hydroxyl group to amine by phthlalimide procedure provided amine **8** in good yield. Coupling of the latter with pheny isocyanate produced the receptor **1** in 41% yields. Similarly, lithocholic acid-based receptor **3** was prepared from reaction of phenyl isocyanate with 3α-(3'-aminopropanoxy)-5β-cholane (**9**), which was obtained from methyl lithocholate. The structures of obtained compounds were characterized by IR, ^1H, ^{13}C NMR, mass spectrometry, and elemental analysis.

The binding ability of **1** and **3** towards selected anions of spherical (F^-, Cl^-, Br^-), Y-shaped ($CH_3CO_2^-$), or tetrahedral ($H_2PO_4^-$) shapes was measured by standard ^1H NMR titration experiments in a $CDCl_3$ solution.[13] All anions were used in the form of tetrabutylammonium (TBA) salts. The addition of equimolar TBACl to the solution of **1** caused significant downfield shifts both the phenyl and alkyl urea -NH- signals by up to $\Delta\delta$ = 1.03 and 0.81 ppm, indicating that anion binding took place via six synchronous hydrogen bonds (N-H$\cdots Cl^-$) operating from the urea moiety. The plot induced chemical shifts versus anion concentration and gave titration curves corresponding to the formation of 1 : 1 complexes (Fig. 2). The stoichiometry of the complexation was also confirmed by measuring the Job plot of **1** with TBACl[14] (Fig. 3). Similar behavior was observed upon addition of all anions used for the screening. From the nonlinear curve fitting EQ NMR program,[15] the association constant of **1** and **3** were determined, and the results are summarized in

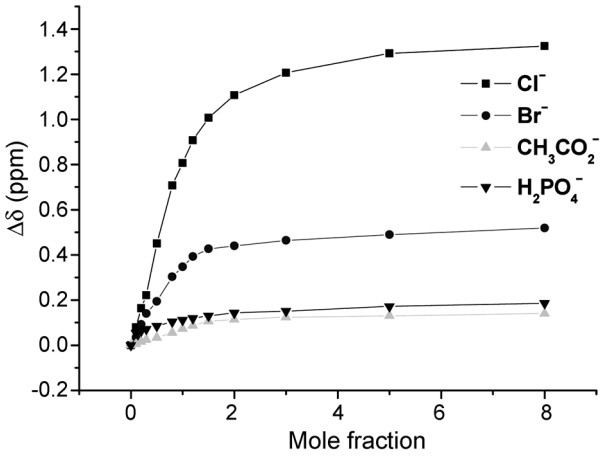


Figure 2. ^1H NMR titration of **1** with various TBA salts.

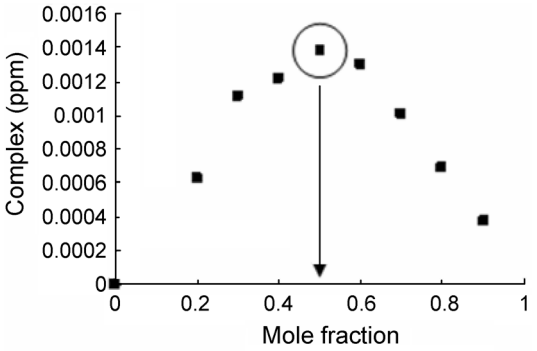


Figure 3. Job plot of **1** with TBACl.

Table 1. Receptors **1** and **3** can bind all anions used irrespective of their shapes. The association constants of **1** showed 7,640, 2,120, 340, 440, and 340 M^{-1} for the binding

Table 1. Association constants (M^{-1}) of receptor **1**, **2**, and **3** obtained from ^1H NMR titrations with various anions

Host	Guest, *Ka*[a]				
	Cl^-	Br^-	I^-	$H_2PO_4^-$	$CH_3CO_2^-$
1	7,640	2,120	340	440	340
2	2,750[b]	1,200[b]	260[b]	4,270[b]	690[b]
3	1,550	430	170	510	NM[c]

[a]Determined in $CDCl_3$, at 25 °C, $[H]_o = 4.5 \times 10^{-3}$ M. Errors estimated to be ≤ 10%. [b]Data were taken from reference 10. [c]NM = not measured.

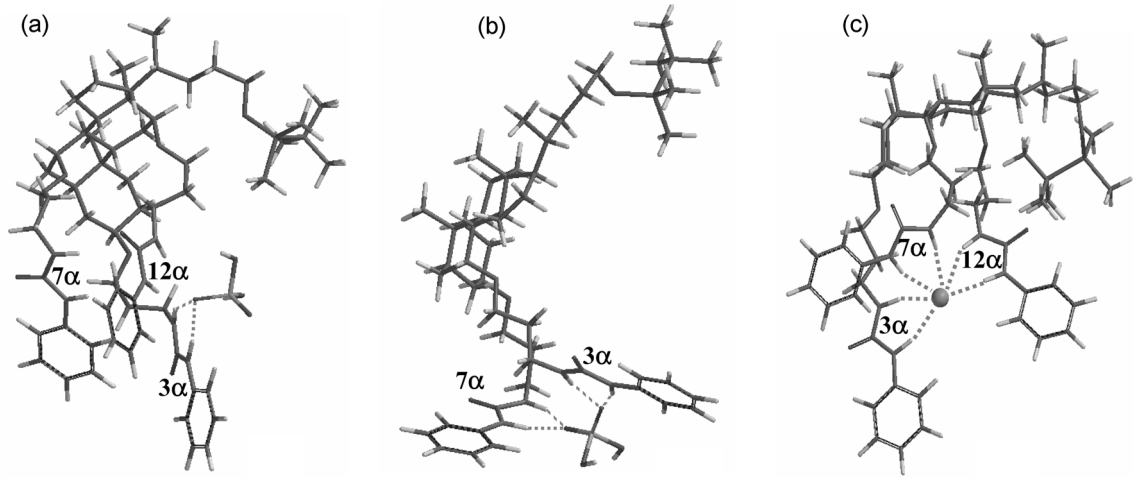


Figure 4. The complex structures of receptor **1** and **2** with anions. (a) **1** with $H_2PO_4^-$, (b) **2** with $H_2PO_4^-$, and (c) **1** with Cl^-.

of Cl^-, Br^-, I^-, $H_2PO_4^-$, and $CH_3CO_2^-$, respectively.

The association constants of **3** revealed 1,550, 430, 170, and 510 M^{-1} for the binding of Cl^-, Br^-, I^-, and $H_2PO_4^-$, respectively. Receptor **1** showed the highest association constant for Cl^- (Ka = 7,640) and modest binding with Br^- (Ka = 2,120). The selectivity of **1** for Cl^- was about 3 times that of Br^-, and over 17 times that for $H_2PO_4^-$. With increasing size/deceasing basicity of halides (except F^-) the association constants regularly diminished. It is obvious that the number of urea moieties dramatically influences anion complexation. For halides, tris(ureido) receptor **1** exhibits much higher binding ability than **2**, possesses two urea units and **3** which bears only one urea unit. These results indicate that the high binding constant was due to cooperative action of six hydrogen-bond donor groups in a receptor.

The surprising fact that bis(ureido) receptor **2** binds phosphate anions (K_a = 4,270 M^{-1}) better than tris(ureido) receptor **1** (K_a = 440 M^{-1}). This result could be explained based on the complex structures of receptors and phosphate ion. The molecular mechanics calculations of complex between **1** and phosphate ion show phosphate ion bind with only 3α-urea N-H protons through hydrogen bonds (distance of N–H $\cdots O^-$ = 1.80-1.87 Å) and one of the 7α-urea N-H proton bind with 12α-urea C=O through hydrogen bond (distance of N–H $\cdots$O=C = 1.86 Å). But in case of **2**, phosphate ion bind to two sets of 3α- and 7α-urea N-H protons through strong hydrogen bonds (estimated distance of N–H $\cdots O^-$ = 1.60-1.73 Å), as shown in Figure 4.[16] The calculated distance of N–H $\cdots O^-$ in **2** with phosphate ion is shorter than that of **1**, suggests that **2** tightly binds with phosphate ion through hydrogen bonds. The calculated distances of N–H $\cdots Cl^-$ in **1** with chloride ion reveal 2.28-2.89 Å.

Further binding studies were carried out by isothermal titration calorimetry (ITC) of **1** with TBAF and TBACl in $CDCl_3$ solution at 15 °C. ITC results in association constant $Ka = 2.26 \times 10^3$ and 4.15×10^3 M^{-1} for F^- and Cl^-, respectively (Table 2). Due to the low detection temperature these association constants from ITC are slightly lower than the values obtained from ^{1}H NMR titration, but are comparable to each other. The association constant of **1** for Cl^- is slightly high than that of F^-.

Table 2. Association constants (M^{-1}) of **1** with TBACl and TBAF obtained from ITC

Host	Guest, K_a[a]	
	F^-	Cl^-
1	2.26×10^3	4.15×10^3

[a]Determined in $CHCl_3$, at 15 °C, $[H]_o = 1.0 \times 10^{-3}$ M, $[G]_o = 1.5 \times 10^{-4}$ M. Error estimated to be ≤15%.

Conclusion

We have shown that newly synthesized cholic acid-based tripodal receptor **1** containing urea pendants selectively recognizes the biologically important chloride ion over other halides and $H_2PO_4^-$. The selectivity of **1** for Cl^- is better than that of **2** and **3**. The selectivity of **1** for Cl^- is about 3 times that of Br^-, and 17 times that for $H_2PO_4^-$.

Experiment Section

General experimental procedures for melting points, FT-IR spectra, mass spectra, high resolution MS, elemental analyses, and TLC analysis and flash chromatography have been described previously.[17] ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker AM-400 spectrometer in a $CDCl_3$ solution. NMR titrations were run at 45 mM concentrations, with aliquots of 0.25 M $(n\text{Bu})_4N^+X^-$ salts solution added. The non-linear curve fittings program (EQ-NMR) was used for curve fittings. Isothermal titration calorimetric (ITC) measurements were performed using an Omega titration microcalorimeter. A 15 mM solution of TBA salt in 40 times (5 μL injection) was added to a 1 mM receptor solution (1.8 mL) in calorimetric cell. Reactions were carried out under an argon atmosphere, and the solution was washed with brine and dried over

anhydrous sodium sulfate. Synthesis of compound **9** will be described elsewhere. Cholic acid and other chemicals were purchased from either Aldrich Chemicals or Fluka Co, and solvents were dried prior to use.

Synthesis of 24-*tert*-butyldimethylsilyloxy-3α,7α,12α-trihydroxy-5β-cholane (5). $LiAlH_4$ (355 mg) was added to a solution of methyl cholate[18] (2.00 g, 4.73 mmol) in dry THF (50 mL) at 0 °C, and stirred for 24 h. The mixture was treated with saturated sodium sulfate solution (3 mL). After the precipitant was removed, the filtrate was dried, and evaporated to dryness. To a solution of the resulting residue, imidazole (644 mg, 9.46 mmol), and catalytic amounts of 4-dimethylaminopyridine (10 mg) in dry CH_2Cl_2 (30 mL) and DMF (50 mL) was added *tert*-butyldimethylsilyl chloride (860 mg, 5.68 mmol) in dry CH_2Cl_2 (10 mL) at room temperature, and stirred for 12 h. The mixture was neutralized with 10% HCl solution and extracted with ethyl acetate, washed, dried, and concentrated. The residue was purified by silica gel chromatography (elution with EtOAc-hexane 3 : 1) to give **5** (1.31 g, 56%) as a solid. Mp 125-127 °C; TLC R_f 0.26 (100% EtOAc); ^{1}H NMR δ 3.93 (s, 1H, 12β-H), 3.79 (s, 1H, 3β-H), 3.53 (t, J = 12.6 Hz, 2H, 24-CH_2), 3.38 (m, 1H, 7β-H), 2.98 (bs, 3H, -OH), 0.93 (d, J = 6.0 Hz, 3H, 21-CH_3), 0.85 (s, 9H, SiC(CH_3)$_3$), 0.84 (s, 3H, 19-CH_3), 0.63 (s, 3H, 18-CH_3), -0.01 (s, 6H, Si(CH_3)$_2$); ^{13}C NMR δ 73.6, 72.3, 68.8, 64.2, 47.8, 46.8, 42.0, 41.9, 39.9, 39.9, 35.9, 35.7, 35.2, 35.1, 32.3, 30.8, 30.0, 28.5, 27.9, 23.6, 22.9, 18.7, 18.1, 12.9, −4.8; Anal. Calcd. for $C_{30}H_{56}O_4Si$: C, 70.81; H, 11.09; Found C, 70.85; H, 11.36.

Synthesis of 24-*tert*-butyldimethylsilyloxy-3α,7α,12α-triallyloxy-5β-cholane (6). NaH (380 mg, 15.72 mmol) was added to a solution of **5** (2.00 g, 3.93 mmol) in dry THF (100 mL) and refluxed for 30 min. Allyl bromide (1.30 mL, 15.72 mmol) was added to the resulting mixture and refluxed for 24 h. After that, additional NaH (380 mg) and allyl bromide (1.30 mL) were added. Following another 24 h refluxing then the solvent was removed, extracted with ethyl acetate, washed, dried and concentrated. The residue was purified by silica gel chromatography (elution with EtOAc-hexane 1 : 10) to give **6** (2.05 g, 83%) as an oil. TLC R_f 0.54 (5% EtOAc-hexane); IR (neat) 3434, 3078, 2926, 2860, 1646, 1463, 1378, 1252, 1094, 1003, 920, 836, 775, 661, 558 cm^{-1}; ^{1}H NMR δ 5.88 (m, 3H, -OCH$_2$C*H*=CH$_2$), 5.21 (m, 3H), 5.05 (m, 3H), 4.01 (m, 2H), 3.95 (d, J = 5.5 Hz, 2H), 3.69 (m, 2H), 3.52 (t, J = 12.6 Hz, 24-CH_2), 3.48 (s, 1H, 12β-H), 3.27 (d, J = 3.0 Hz, 1H, 3β-H), 3.09 (m, 1H, 7β-H), 0.87 (d, J = 6.5 Hz, 3H, 21-CH_3), 0.85 (s, 12H, SiC(CH_3)$_3$ and 19-CH_3), 0.61 (s, 3H, 18-CH_3), −0.03 (s, 6H, Si(CH_3)$_2$); ^{13}C NMR δ 135.9, 116.3, 115.8, 115.4, 115.1, 80.5, 80.6, 79.1, 78.9, 74.8, 74.5, 69.2, 68.6, 64.0, 63.8, 63.6, 46.2, 42.4, 41.9, 41.8, 35.4, 34.9, 31.8, 29.5, 28.5, 27.4, 26.1, 26.0, 25.9, 23.1, 22.9, 18.3, 17.8, 17.6, 12.5, 12.4, −5.3; Anal. Calcd. for $C_{39}H_{68}O_4Si$: C, 74.47; H, 10.90; Found C, 74.62; H, 10.83.

Synthesis of 24-*tert*-butyldimethylsilyloxy-3α,7α,12α-tri(3'-hydroxypropanoxy)-5β-cholane (7). 0.5 M solution of 9-BBN (12.7 mL) in THF was added to a solution of **5** (1.00 g, 1.59 mmol) in dry THF (100 mL) at −78 °C and stirred at room temperature for 12 h. The mixture was quenched with 20% NaOH solution (5 mL) and 30% hydrogen peroxide (5 mL) sequentially, and refluxed for 1 h. The solvent was removed, it was extracted with ethyl acetate, washed, dried, and concentrated. The residue was purified by silica gel chromatography (elution with EtOAc-hexane 3 : 1) to give **7** (575 mg, 53%) as an oil. TLC R_f 0.20 (100% EtOAc); IR (neat) 3358, 2930, 1550, 1463, 1369, 1255, 1094, 835, 737 cm^{-1}; ^{1}H NMR δ 3.74-3.51 (m, 14H), 3.46 (s, 1H), 3.38 (s, 4H), 3.27 (bs, 1H), 3.23 (s, 1H), 3.14 (bs, 2H), 0.85 (s, 15H, 19-CH_3, 21-CH_3, and SiC(CH_3)$_3$), 0.61 (s, 3H, 18-CH_3), −0.01 (s, 6H, Si(CH_3)$_2$); ^{13}C NMR δ 80.7, 79.1, 76.6, 66.9, 66.4, 66.1, 66.0, 64.1, 63.7, 61.8, 61.7, 61.5, 47.2, 46.9, 46.3, 42.9, 42.9, 39.9, 35.7, 35.6, 35.2, 35.2, 33.1, 32.7, 32.6, 32.2, 32.1, 29.9, 29.6, 29.1, 27.9, 27.8, 27.4, 26.3, 26.0, 23.7, 23.0, 22.6, 18.4, 12.8, −3.2, −4.8; HRFAB (EI) Calcd for $C_{39}H_{74}O_7Si$: 683.0799, Found: 683.0826.

Synthesis of cholic-urea receptor (1). Phthalimide (900 mg, 5.86 mmol) and triphenyl phosphine (1.43 g, 5.86 mmol, 8 eq) were added to a solution of **7** (500 mg, 0.73 mmol) in dry THF (50 mL). After 10 min, diethyl azodicarboxylate (0.9 mL, 5.86 mmol) was added to the mixture and stirred at room temperature for 12 h. Then the solvent was removed, and it was extracted with ethyl acetate, washed, dried, and concentrated. Without further purification, the residue (0.82 mmol) and hydrazine monohydrate (365 mg, 7.3 mmol) were refluxed in ethanol for 24 h. After the solvent was removed, it was extracted with ethyl acetate, washed, dried, and concentrated. The residue was purified by column chromatography (elution with CH_2Cl_2-MeOH-NH_4OH 16 : 3 : 0.5) to yield crude amine **8** (240 mg). Phenyl isocyanate (0.21 mL) was reacted with **8** (240 mg) in dry $CHCl_3$ (20 mL) at room temperature for 5 h. Then the solvent was removed, extracted, washed, dried, and concentrated. The residue was purified by column chromatography (elution with EtOAc-hexane 1 : 1) to give **1** (310 mg, 41%) as a solid. Mp 109-110 °C (CH_2Cl_2-hexane); TLC R_f 0.48 (EtOAc-hexane 1 : 1); IR (KBr) 3441, 2929, 2252, 2125, 1659, 1028, 824, 762, 626 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (t, J = 14.5 Hz, 3H), 7.37 (d, J = 8.0 Hz, 6H), 7.18 (m, 6H), 6.86 (m, 3H), 6.12 (m, 3H), 3.58-3.49 (m, 4H), 3.46 (bs, 1H), 3.40 (t, J = 11.5 Hz, 2H), 3.23-3.08 (m, 9H), 3.02 (m, 1H), 0.89 (d, J = 6.5 Hz, 3H, 21-CH_3), 0.86 (s, 3H, 19-CH_3), 0.84 (s, 9H, SiC(CH_3)$_3$), 0.63 (s, 3H, 18-CH_3), −0.01 (s, 6H, Si(CH_3)$_2$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.6, 155.5, 140.9, 131.8, 128.9, 128.9, 128.8, 121.2, 117.9, 80.6, 78.9, 75.6, 65.9, 65.1, 63.2, 46.4, 46.2, 42.9, 41.3, 40.5, 36.9, 36.8, 34.8, 30.7, 26.1, 23.1, 18.2, 18.1, 12.7, −4.9; Anal. Calcd. for $C_{60}H_{92}N_6O_7Si$: C, 69.46; H, 8.94; N, 8.10; Found C, 69.29; H, 8.92; N, 8.17.

Synthesis of lithocholic-urea receptor (3). This compound was obtained in a 92% yield from **9** and phenyl isocyanate. Mp 93-95 °C (CH_2Cl_2-hexane); TLC R_f 0.50 (EtOAc-hexane 1 : 2); IR (KBr) 3331, 2934, 2863, 1651, 1555, 1444, 1312, 1237, 836, 752 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.33-6.91 (m, 5H), 5.63 (s, 1H), 3.57-3.36 (m, 6H), 3.17 (s, 1H, 3β-H), 0.90 (s, 6H, 19- and 21-

CH_3), 0.87 (s, 9H, SiC(CH_3)$_3$), 0.63 (s, 3H, 18-CH_3), −0.03 (s, 6H, Si(CH_3)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 156.4, 138.6, 129.2, 123.6, 123.0, 121.1, 120.0, 79.4, 66.3, 63.8, 56.4, 56.2, 42.6, 42.0, 40.3, 40.1, 38.7, 35.8, 35.5, 35.2, 34.8, 33.1, 31.9, 30.0, 29.5, 28.2, 27.2, 26.3, 26.0, 24.2, 23.4, 20.8, 18.6, 12.0, −5.3; Anal. Calcd. for $C_{40}H_{68}N_2O_3Si$: C, 73.57; H, 10.50; N, 4.29; Found C, 73.31; H, 10.55; N, 4.00.

Acknowledgments. This work was supported by grant from the KOSEF (R05-2001-000-00227-0) and the BK21 program.

References and Notes

1. (a) Bianch, A.; Bowman-James, K.; García-España, E., *Supramolecular Chemistry of Anions*; Wiley-VCH: New York, 1997. (b) Schmidtchen, F. P.; Berger, M. *Chem. Rev.* **1997**, *97*, 1609. (c) Bühlmann, P.; Pretsch, E.; Bakker, E. *Chem. Rev.* **1998**, *98*, 1593. (d) Antonisse, M. M. G.; Reinhoudt, D. N. *Electroanalysis* **1999**, *11*, 1035. (e) Beer, P. D.; Gale, P. A. *Angew. Chem. Int. Ed.* **2001**, *40*, 487. (f) Gale, P. A. *Coord. Chem. Rev.* **2003**, *240*, 191.
2. Kirk, K. L. *Biochemistry of the Halogens and Inorganic Halides*; Plenum Press: New York, 1991.
3. Broughman, J. R.; Shank, L. P.; Takeguchi, W.; Schultz, B. D.; Iwamoto, T.; Mitchell, K. E.; Tomich, J. M. *Biochemistry* **2002**, *41*, 7350 and references therein.
4. (a) Capitán-Vallvey, L. F.; Guerrero, E. A.; Merelo, C. B.; Ramos, M. D. F. *Anal. Bioanal. Chem.* **2004**, *380*, 563. (b) Bratov, A.; Abramova, N.; Domínguez, C. *Anal. Chim. Acta* **2004**, *514*, 99. (c) Xu, C.; Qin, Y.; Bakker, E. *Talanta* **2004**, *63*, 180. (d) Yang, D.; Qu, J.; Li, W.; Zhang, Y.-H.; Ren, Y.; Wang, D.-P.; Wu, Y.-D. *J. Am. Chem. Soc.* **2002**, *124*, 12410.
5. (a) Matile, S.; Som, A.; Sorde, N. *Tetrahedron* **2004**, *60*, 6405. (b) McNally, B. A.; Koulov, A. V.; Smith, B. D.; Joos, J.-B.; Davis, A. P. *Chem. Commun.* **2005**, 1087. (b) Koulov, A. V.; Lambert, T. N.; Shukla, R.; Jain, M.; Boon, J. M.; Smith, B. D.; Li, H.; Sheppard, D. N.; Joos, J.-B.; Clare, J. P.; Davis, A. P. *Angew. Chem. Int. Ed.* **2003**, *42*, 4931. (c) Schlesinger, P. H.; Ferdani, R.; Pajewski, R.; Pajewski, J.; Gokel, G. W. *Chem. Commun.* **2002**, 840.
6. For reviews, see: (a) Davis, A. P.; Joos, J.-B. *Coord. Chem. Rev.* **2003**, *240*, 143. (b) Urata, K.; Takaishi, N. *Eur. J. Lipid Sci. Technol.* **2001**, *103*, 29. (c) Wallimann, P.; Marti, T.; Fürer, A.; Diederich, F. *Chem. Rev.* **1997**, *97*, 1567. (d) Davis, A. P.; Gilmer, J. F.; Perry, J. J. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1312. (e) Davis, A. P. *Chem. Soc. Rev.* **1993**, *22*, 243.
7. (a) Maulucci, N.; De Riccardis, F.; Botta, C. B.; Casapullo, A.; Cressina, E.; Fregonese, M.; Tecilla, P.; Izzo, I. *Chem. Commun.* **2005**, 1354. (b) Kolehmainen, E.; Koivukorpi, J.; Sievänen, E.; Král, V. *Supramol. Chem.* **2005**, *17*, 437.
8. Davis, A. P.; Perry, J. J.; Williams, R. P. *J. Am. Chem. Soc.* **1997**, *119*, 1793.
9. (a) Ayling, A. J.; Pérez-Payán, M. N.; Davis, A. P. *J. Am. Chem. Soc.* **2001**, *123*, 12716. (b) Ayling, A. J.; Broderick, S.; Clare, J. P.; Davis, A. P.; Pérez-Payán, M. N.; Lahtinen, M.; Nissinen, M. J.; Rissanen, K. *Chem Eur. J.* **2002**, *8*, 2197. (c) Sisson, A. L.; Clare, J. P.; Taylor, L. K.; Charmant, J. P. H.; Davis, A. P. *Chem. Commun.* **2003**, 2246. (d) Shim, J. H.; Jeong, I. S.; Lee, M. H.; Hong, H. P.; On, J. H.; Kim, K. S.; Kim, H.-S.; Kim, B. H.; Cha, G. S.; Nam, H. *Talanta* **2004**, *63*, 61. (e) Clare, J. P.; Ayling, A. J.; Joos, J.-B.; Sisson, A. L.; Magro, G.; Pérez-Payán, M. N.; Lambert, T. N.; Shukla, R.; Smith, B. D.; Davis, A. P. *J. Am. Chem. Soc.* **2005**, *127*, 10739.
10. Kim, K. S.; Kim, H.-S. *Bull. Korean Chem. Soc.* **2004**, *25*, 1411.
11. Kim, K. S.; Kim, H.-S. *Tetrahedron* **2005**, *61*, 12366.
12. For selected examples of urea based receptors, see: (a) Boiochi, M.; Boca, L. D.; Gómez, E. D.; Fabbrizzi, L.; Licchelli, M.; Monzani, E. *J. Am. Chem. Soc.* **2004**, *126*, 16507. (b) Cho, E. J.; Ryu, B. J.; Lee, Y. J.; Nam, K. C. *Org. Lett.* **2005**, *7*, 2607, and references therein.
13. Fielding, L. *Tetrahedron* **2000**, *56*, 6151.
14. (a) Job, P. *Compt. Rend.* **1925**, *180*, 928. (b) Blanda, M. T.; Horner, J. H.; Newcomb, M. *J. Org. Chem.* **1989**, *54*, 4626.
15. (a) Hynes, M. J. *J. Chem. Soc. Dalton Trans.* **1993**, 311. (b) Connors, K. A. *Binding Constants*; Wiley: New York, 1987.
16. MP2 calculation at the AM1 mode level was performed SPARTAN'04 for Windows (Wavefunction, Inc.: Irvine, CA)
17. Kim, H.-S.; Choi, B.-S.; Kwon, K.-C.; Lee, S.-O.; Kwak, H. J.; Lee, C. H. *Bioorg. Med. Chem.* **2000**, *8*, 2059.
18. Savage, P. B.; Allman, G. W.; Willardson, B. M.; Driscoll, C. D.; Budge, L. P.; Li, C. *J. Am. Chem. Soc.* **1999**, *121*, 931.