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ORIGINAL ARTICLE

Diphenylmethane-based anion receptors bearing bis(*p*-toluenesulfonyl urea) groups

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Abstract Diphenylmethane-based receptors (**1**) bearing urea units were prepared for anion recognition. Analogous anion receptors based on biphenyl (**2**), diphenylsulfide (**3**), cyclophane (**4**) and phenyl (**5**) were also synthesized as control compounds. Their anion recognition ability was evaluated by ^{1}H NMR spectroscopy in $CDCl_3$ at 297 K. The association constants for the complexation between receptors and anions are strongly dependent on the framework of the receptors and the urea moiety substituent. The much stronger binding of a chloride anion by the diphenylmethane-based receptor (**1a**) having two *p*-toluenesulfonyl urea groups was observed. It is rationalized by the stronger hydrogen bond donor strength of the *p*-toluenesulfonyl urea group and the moderate flexibility of the diphenylmethane framework and is explained in terms of the complex geometry.

Keywords Anion recognition · Chloride anion selectivity · Diphenylmethane · Quaternary ammonium salt · *p*-Toluenesulfonyl urea

Introduction

The design and synthesis of systems that are capable of sensing various biologically and/or chemically important negatively charged species is an area of current interest [1]. A variety of artificial anion receptors coordinate anions by amide, urea and thiourea groups, which have been introduced into a rigid framework, because the structural rigidity of a receptor is usually effective in anion selectivity and also produces higher affinity toward an anion [2]. Although the structural flexibility of receptors generally becomes a small association constant, the introduction of the recognition site into the appropriate position advantageously affect the enthalpy [3]. Consequently, it will be possible to efficiently and selectively bind anions even using a flexible structure. Therefore, we conceived the idea to use diphenylmethane as a backbone of the anion receptor because this skeleton combines a moderate rigidity with flexibility. In this paper, we report the synthesis and anion binding properties of the diphenylmethane-based anion receptor bearing urea groups. To clarify the importance of the diphenylmethane moiety regarding the anion recognition, we synthesized the analogous urea derivatives based on the biphenyl, diphenylsulfide, cyclophane and phenyl and investigated their anion binding abilities (Fig. 1).

Experimental

Melting points were measured by Stuart SMP3 melting point apparatus and were not corrected. ^{1}H and ^{13}C NMR spectra were measured by Varian INOVA 500 (500 MHz for ^{1}H, 125 MHz for ^{13}C) and/or Varian Mercury 200 (200 MHz for ^{1}H, 50 MHz for ^{13}C) spectrophotometers using tetramethylsilane as an internal standard. Fab-mass spectra were collected by JEOL AX-505HA spectrometer using *m*-nitrobenzyl alcohol as a matrix. IR spectra were recorded on FORIBA FT-720 spectrophotometer. All chemicals were reagent grade and were used without

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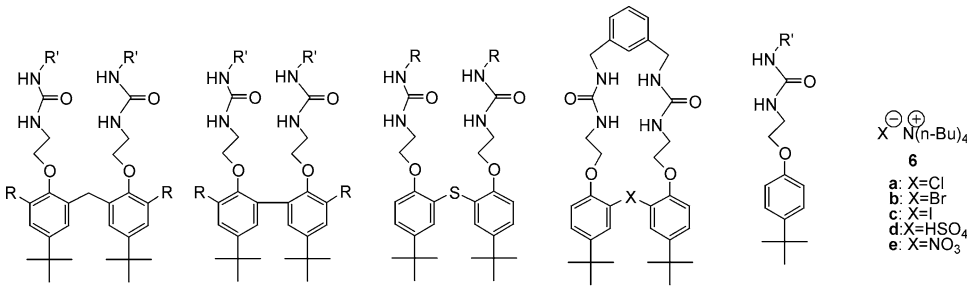


Fig. 1 Urea based anion receptors (**1**, **2**, **3**, **4** and **5**) and quaternary ammonium salts (**6**)

further purification. Chloroacetonitrile, phenyl isocyanate, *p*-toluenesulfonyl isocyanate, *m*-xylylene diisocyanate, sodium iodide, potassium carbonate and lithium aluminium hydride were purchased from Kanto Chemical Co., Tokyo Kasei Industry and Aldrich. Compounds of bis(2-hydroxy-5-*t*-butylphenyl)methane (**7a**) [4], bis(2-hydroxy-3,5-di-*t*-butyl)methane (**7b**) [5], bis(2-hydroxy-5-*t*-butylphenyl) sulfide (**8**) [6], 2,2′-dihydroxy-5,5′-di-*t*-butyl biphenyl (**13a**) [7] and 2,2′-dihydroxy-3,3′,5,5′-tetra-*t*-butyl biphenyl (**13b**) [7] were prepared according to literature reported previously.

General procedure for the preparation of nitrile derivatives (9, 10 and 14)

To a solution of **7**, **8** or **13** (20 mmol) in dry acetone (100 mL) was added potassium carbonate (11.1 g, 80 mmol), sodium iodide (13.2 g, 88 mmol), and chloroacetonitrile (6.04 g, 80 mmol) was added, and then the mixture was refluxed for 12–72 h. After cooling to room temperature, the precipitate was filtered off. The filtrate was condensed by rotary evaporator to give red brown oily residue, which was dissolved with chloroform (200 mL). The solution was washed with water, 10% sodium thiosulfate aqueous solution, and brine. Organic layer was separated and dried over anhydrous sodium sulfate. Removal of solvent gave oily residue, which was subjected to column chromatography on silica gel (chloroform:hexane 2:1 (**9a**), ethyl acetate:hexane 1:20 (**9b**), ethyl acetate:hexane 3:1 (**10**), chloroform:hexane 2:1 (**14a**), chloroform:hexane, 1:1 (**14b**)) to give nitrile derivatives (**9**, **10** and **14**) as colorless crystals.

9a: 40% yield. melting point 91–93 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (s, *t*-Bu × 2, 18H), 3.97 (s, $ArCH_2Ar$, 2H), 4.73 (s, CH_2 × 2, 4H), 6.86 (d, Ar–H × 2, 2H, J = 8.6 Hz), 7.17 (d, Ar–H × 2, 2H, J = 2.4 Hz), 7.24 (dd, Ar–H × 2, 2H, J = 2.4, 8.6 Hz). ^{13}C-NMR ($CDCl_3$) δ: 31.3, 34.6, 35.3, 58.0, 115.5, 123.1, 126.5, 132.0, 142.2, 147.5, 152.9. FAB-MS: 391 $(M + H)^+$. Anal. Calcd for $C_{25}H_{30}N_2O_2$: C, 76.89%; H, 7.74%; N, 7.17%. Found: C, 76.84%; H, 7.54%; N, 6.92%.

9b: 39% yield. melting point 92–93 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (*t*-Bu × 2, 18H), 1.43 (s, *t*-Bu × 2, 18H), 4.08 (s, $ArCH_2Ar$, 2H), 4.53 (s, CH_2 × 2, 4H), 6.90 (d, Ar–H × 2, 2H, J = 2.6 Hz), 7.27 (d, Ar–H × 2, 2H, J = 2.6 Hz). ^{13}C-NMR ($CDCl_3$) δ: 31.2, 31.3, 34.6, 35.3, 35.4, 58.0, 115.5, 123.1, 126.5, 132.0, 142.2, 147.5, 152.9. FAB-MS: 503 $(M + H)^+$. Anal. Calcd for $C_{33}H_{46}N_2O_2$: C, 78.84%; H, 9.22%; N, 5.57%. Found: C, 78.74%; H, 9.33%; N, 5.32%.

10: 62% yield. melting point 70- 71 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (s, *t*-Bu × 2, 18H), 4.80 (s, CH_2 × 2, 4H), 7.01 (d, Ar–H × 2, 2H, J = 9.0 Hz), 7.15 (d, Ar–H × 2, 2H, J = 2.0 Hz), 7.32 (dd, Ar–H × 2, 2H, J = 2.0, 9.0 Hz). ^{13}C-NMR ($CDCl_3$) δ: 31.0, 34.2, 54.4, 113.7, 115.0, 123.3, 125.6, 129.9, 147.0, 152.5. FAB-MS: 409 $(M + H)^+$. Calcd for $C_{24}H_{28}N_2O_2S$: C, 70.55%; H, 6.91%; N, 6.86%. Found: C, 70.60%; H, 7.10%; N, 6.88%.

14a: 62% yield. melting point 140-141 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.35 (s, *t*-Bu × 2, 18H), 4.70 (s, CH_2 × 2, 4H), 7.01 (d, Ar–H × 2, 2H, J = 9.0 Hz), 7.31 (d, Ar–H × 2, 2H, J = 2.5 Hz), 7.42 (dd, Ar–H × 2, 2H, J = 2.5, 9.0 Hz). ^{13}C-NMR ($CDCl_3$) δ: 31.4, 34.3, 54.0, 112.5, 115.4, 125.9, 127.8, 129.2, 146.1, 151.6. FAB-MS: 377 $(M + H)^+$. Anal. Calcd for $C_{24}H_{28}N_2O_2$: C, 76.56%; H, 7.50%; N, 7.74%. Found: C, 76.62%; H, 7.44%; N, 7.52%.

14b: 84% yield. melting point 164–165 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.35 (s, *t*-Bu × 2, 18H), 1.46 (s, *t*-Bu × 2, 18H), 3.98 (s, CH_2 × 2, 4H), 7.24 (d, Ar–H × 2, 2H, J = 2.6 Hz), 7.44 (d, Ar–H × 2, 2H, J = 2.6 Hz). ^{13}C-NMR ($CDCl_3$) δ: 30.8, 31.4, 34.7, 35.4, 56.1, 115.0, 124.5, 126.7, 130.7, 142.7, 147.8, 151.6. FAB-MS: 489 $(M + H)^+$. Anal. Calcd for $C_{32}H_{44}N_2O_2$: C, 78.65%; H, 9.07%; N, 5.73%. Found: C, 78.77%; H, 8.82%; N, 5.53%.

General procedure for the preparation of acyclic di-urea derivatives (1, 2 and 3) and mono-urea derivatives (5)

To a solution of nitrile derivative (**9**, **10** or **14**) (3.0 mmol) in dry ether (30 mL), lithium aluminum hydride (12 mmol) was added in small portions at room temperature. After the addition was complete, the mixture was refluxed for 4 h. After the reaction flask was immersed into an ice-water

bath, the excess lithium aluminium hydride was destroyed by careful addition of wet benzene and water. The solid was filtered off. The organic layer was separated, and the water layer was extracted with benzene. The combined organic layers were dried over anhydrous sodium sulfate. Removal of solvent gave amine derivatives (**11**, **12** or **15**) as an oily residue, which was dissolved with dry benzene (20 mL). To the benzene solution was added phenyl isocyanate (643 mg, 5.4 mmol) or *p*-toluenesulfonyl isocyanate (1.06 g, 5.4 mmol) at room temperature, and the mixture was stirred at room temperature for 12 h. The precipitate of the acyclic bis-urea derivatives (**1**, **2**, and **3**) were collected by filtration. Mono-urea derivatives (**5**) were also synthesized by adopting above procedure.

1a: 22% yield. melting point 122–123 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (s, *t*-Bu × 2, 18H), 2.33 (s, CH_3 × 2, 6H), 3.54 (m, CH_2 × 2, 4H), 3.87 (s, CH_2, 2H), 3.92 (t, CH_2 × 2, 4H, J = 4.6 Hz), 6.51 (s, NH × 2, 2H), 6.72 (d, Ar–H × 2, 2H, J = 8.8 Hz), 7.00 (d, Ar–H × 2, 2H, J = 2.0 Hz), 7.10 (d, Ar–H × 4, 4H, J = 8.0 Hz), 7.20 (dd, Ar–H × 2, 2H, J = 8.8, 2.0 Hz), 7.76 (d, Ar–H × 4, 4H, J = 8.0 Hz), 8.40 (bs, NH × 2, 2H). ^{13}C-NMR ($CDCl_3$) δ: 21.6, 29.3, 31.5, 34.1, 39.7, 67.0, 110.9, 123.5, 127.3, 127.5, 128.4, 129.7, 136.4, 143.5, 144.4, 152.2, 154.1. IR ($CHCl_3$): 3390 (ν_{NH}), 1670 (ν_{CO}) cm^{-1}. FAB-MS: 793 (M + H)$^+$. Anal. Calcd for $C_{41}H_{52}N_4O_8S_2$: C, 62.10%; H, 6.61%; N, 7.07%. Found: C, 62.28%; H, 6.80%; N, 6.82%.

1c: 33% yield. melting point 125–126 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (s, *t*-Bu × 2, 18H), 3.59 (m, CH_2 × 2, 4H), 3.95 (t, CH_2 × 2, 4H, J = 4.8 Hz), 3.99 (s, $ArCH_2Ar$, 2H), 5.22 (bs, NH × 2, 1H), 6.76 (d, Ar–H × 2, 2H, J = 8.6 Hz), 6.90 (bs, NH × 2, 2H), 6.95-7.06 (m, Ar–H × 4, 5H), 7.15-7.24 (m, Ar–H × 10, 10H). ^{13}C-NMR ($CDCl_3$) δ: 30.0, 31.4, 34.1, 39.7, 68.1, 111.3, 120.3, 123.1, 123.5, 127.6, 128.8, 129.0, 138.8, 143.6, 154.3, 156.3. IR ($CHCl_3$): 3330 (ν_{NH}), 1649 (ν_{CO}) cm^{-1}. FAB-MS: 637 (M + H)$^+$. Anal. Calcd for $C_{39}H_{48}N_4O_4$: C, 73.56%; H, 7.60%; N, 8.80%. Found: C, 73.66%; H, 7.55%; N, 8.72%.

1d: 44% yield. melting point 138–139 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (s, *t*-Bu × 2, 18H), 1.39 (s, *t*-Bu × 2, 18H), 3.60 (m, CH_2 × 2, 4H), 3.83 (t, CH_2 × 2, 4H, J = 4.4 Hz), 4.03 (s, $ArCH_2Ar$, 2H), 5.95 (bs, NH × 2, 2H), 6.87 (bs, NH × 2, 2H), 6.95–7.25 (m, Ar–H × 14, 14H). ^{13}C-NMR ($CDCl_3$) δ: 31.3, 31.4, 34.5, 35.3, 35.4, 40.8, 72.1, 111.1, 120.8, 122.3, 123.4, 129.0, 133.0, 138.6, 141.5, 145.8, 153.7, 156.9. IR ($CHCl_3$): 3338 (ν_{NH}), 1649 (ν_{CO}) cm^{-1}. FAB-MS: 749 (M + H)$^+$. Anal. Calcd for $C_{47}H_{64}N_4O_4$: C, 75.36%; H, 8.61%; N, 7.48%. Found: C, 75.42%; H, 8.72%; N, 7.33%.

2a: 24% yield. melting point 109 °C (decomposition). ^{1}H-NMR ($CDCl_3$) δ: 1.31 (s, *t*-Bu × 2, 18H), 2.43 (s, CH_3 × 2, 6H), 3.32 (m, CH_2 × 2, 4H), 3.79 (t, CH_2 × 2, 4H, J = 5.4 Hz), 6.26 (s, NH × 2, 2H), 6.77 (d, Ar–H × 2, 2H, J = 8.0 Hz), 7.25 (d, Ar–H × 2, 2H, J = 2.0 Hz)7.27 (d, Ar–H × 2, 2H, J = 8.0 Hz), 7.27 (dd, Ar–H × 4, 4H, J = 8.0, 2.0 Hz), 7.82 (d, Ar–H × 4, 4H, J = 8.0 Hz), 8.695(s, NH × 2, 2H). ^{13}C-NMR ($CDCl_3$) δ: 21.6, 31.5, 34.2, 39.9, 68.5, 114.1, 125.3, 127.2, 127.4, 128.8, 129.8, 136.4, 144.4, 144.6, 152.1, 153.7. IR ($CHCl_3$): 3390 (ν_{NH}), 1680 (ν_{CO}) cm^{-1}. FAB-MS: 779 (M + H)$^+$. Anal. Calcd for $C_{40}H_{50}N_4O_8S_2$: C, 61.67%; H, 6.47%; N, 7.19%. Found: C, 61.72%; H, 6.32%; N, 6.91%.

2c: 27% yield. melting point 230–231 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.13 (s, *t*-Bu × 2, 18H), 3.40 (m, CH_2 × 2, 4H), 3.92 (t, CH_2 × 2, 4H, J = 5.0 Hz), 5.73 (bs, NH × 2, 2H), 6.74 (bs, NH × 2, 2H), 6.86 (d, Ar–H × 2, 2H, J = 8.5 Hz), 6.90 (m, Ar–H × 2, 2H), 7.15 (m, Ar–H × 4, 4H), 7.22–7.27 (m, Ar–H × 8, 8H). ^{13}C-NMR ($CDCl_3$) δ: 31.4, 34.1, 39.7, 69.0, 113.6, 119.0, 119.1, 122.1, 125.1, 128.7, 128.8, 139.4, 144.0, 153.9, 156.2. IR ($CHCl_3$): 3338 (ν_{NH}), 1650 (ν_{CO}) cm^{-1}. FAB-MS: 623 (M + H)$^+$. Anal. Calcd for $C_{38}H_{46}N_4O_4$: C, 73.28%; H, 7.44%; N, 9.00%. Found: C, 73.01%; H, 7.72%; N, 8.80%.

2d: 25% yield. melting point 240–241 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (s, *t*-Bu × 2, 18H), 1.31 (s, *t*-Bu × 2, 18H), 3.05 (m, CH_2, 2H), 3.33 (m, CH_2 × 2, 4H), 3.41 (m, CH_2, 2H), 5.56 (bs, NH × 2, 2H) 6.87 (m, Ar–H × 2, 2H), 7.03 (bs, NH × 2, 2H), 7.03–7.15 (m, Ar–H × 10, 10H), 7.26 (d, Ar–H × 2, 2H, J = 2.0 Hz). ^{13}C-NMR ($CDCl_3$) δ: 31.0, 31.5, 34.5, 35.4, 40.3, 69.9, 120.8, 123.2, 123.6, 127.8, 129.0, 133.1, 138.9, 141.6, 145.4, 152.9, 156.4. IR ($CHCl_3$): 3338 (ν_{NH}), 1653 (ν_{CO}) cm^{-1}. FAB-MS: 735 (M + H)$^+$. Anal. Calcd for $C_{46}H_{62}N_4O_4$: C, 75.17%; H, 8.50%; N, 7.62%. Found: C, 75.20%; H, 8.42%; N, 7.50%.

3a: 18% yield. melting point 120–121 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (s, *t*-Bu × 2, 18H), 2.35 (s, CH_3 × 2, 6H), 3.51 (m, CH_2 × 2, 4H), 3.98 (t, CH_2 × 2, 4H, J = 5.0 Hz), 6.40 (s, NH × 2, 2H), 6.798(d, Ar–H × 4, 4H, J = 8.4 Hz), 7.12 (d, Ar–H × 2, 2H, J = 2.4 Hz), 7.17 (d, Ar–H × 2, 2H, J = 8.4 Hz), 7.22 (dd, Ar–H × 2, 2H, J = 8.4, 2.4 Hz), 7.83 (d, Ar–H × 4, 4H, J = 8.4 Hz), 8.60 (s, NH × 2, 2H). ^{13}C-NMR ($CDCl_3$) δ: 21.5, 31.3, 34.2, 39.7, 68.2, 112.9, 123.2, 125.1, 127.5, 128.9, 129.7, 136.4, 144.4, 145.0, 152.1, 154.3. IR ($CHCl_3$): 3388 (ν_{NH}), 1688 (ν_{CO}) cm^{-1}. FAB-MS: 811 (M + H)$^+$. Anal. Calcd for $C_{40}H_{50}N_4O_8S_3$: C, 59.24%; H, 6.21%; N, 6.91%. Found: C, 59.12%; H, 6.32%; N, 6.70%.

3b: 11% yield. melting point 99–100 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (s, *t*-Bu × 2, 18H), 3.46 (m, CH_2 × 2, 4H), 4.01 (t, CH_2 × 2, 4H, J = 5.0 Hz), 5.43 (s, NH × 2, 2H), 6.85 (d, Ar–H × 2, 2H, J = 8.0 Hz), 6.92 (s, NH × 2, 2H), 6.97 (t, Ar–H × 2, 2H, J = 7.0 Hz), 7.13 (d, Ar–H × 2, 2H, J = 2.0 Hz), 7.18 (dd, Ar–H × 4, 4H, J = 7.0, 8.0 Hz), 7.24 (d, Ar–H × 4, 4H, J = 8.0 Hz), 7.25 (dd, Ar–H × 2, 2H, J = 2.0, 8.0 Hz). ^{13}C-NMR ($CDCl_3$) δ: 31.3, 34.3, 39.8, 69.7, 113.8, 120.1, 123.1, 123.3, 125.3, 128.9, 129.0, 138.7, 145.3, 154.4, 156.1. IR ($CHCl_3$): 3349 (ν_{NH}), 1671 (ν_{CO}) cm^{-1}. FAB-MS: 655 (M + H)$^+$. Anal. Calcd for

$C_{38}H_{46}N_4O_4S$: C, 69.70%; H, 7.08%; N, 8.56%. Found: C, 69.90%; H, 7.11%; N, 8.32%.

5a: 50% yield. melting point 184–185 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (s, *t*-Bu, 9H), 2.31 (s, CH_3, 3H), 3.64 (m, CH_2, 2H), 3.92 (t, CH_2, 2H, $J = 5.2$ Hz), 6.84 (d, Ar–H, 1H × 2, $J = 8.8$ Hz), 7.01 (d, Ar–H, 1H × 2, $J = 8.4$ Hz), 7.10 (s, NH, 1H), 7.34 (d, Ar–H, 1H × 2, $J = 8.8$ Hz), 7.71 (d, Ar–H, 1H × 2, $J = 8.4$ Hz), 7.82 (s, NH, 1H). ^{13}C-NMR ($CDCl_3$) δ: 21.5, 31.5, 34.1, 39.7, 66.5, 113.9, 126.3, 127.0, 129.8, 136.4, 144.0, 144.6, 152.0, 156.0. IR ($CHCl_3$): 3360 (ν_{NH}), 1647 (ν_{CO}) cm^{-1}. FAB-MS: 391 $(M + H)^+$. Anal. Calcd for $C_{20}H_{26}N_2O_4S$: C, 61.51%; H, 6.71%; N, 7.17%. Found: C, 61.44%; H, 6.88%; N, 6.89%.

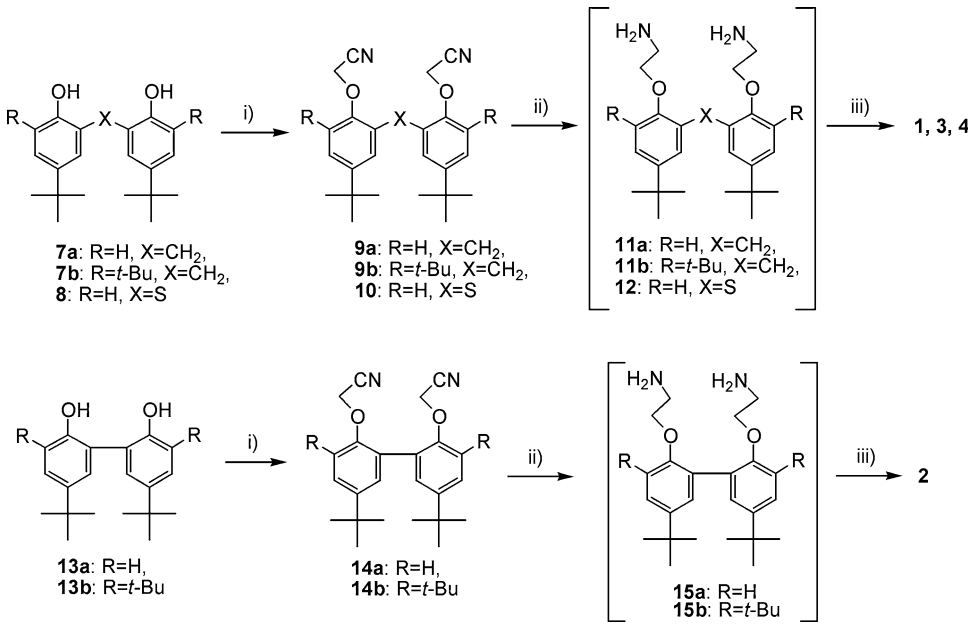
5b: 42% yield. melting point 153–154 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (s, *t*-Bu, 9H), 3.65 (m, CH_2, 2H), 4.08 (t, CH_2, 2H, $J = 4.8$ Hz), 5.20 (bs, NH, 1H), 6.40 (bs, NH, 1H), 6.82 (m, Ar–H × 2, 2H), 7.10 (m, Ar–H, 1H), 7.25-7.36 (m, Ar–H × 6, 6H). ^{13}C-NMR ($CDCl_3$) δ: 31.5, 34.0, 39.8, 67.5, 114.0, 120.7, 123.5, 126.3, 129.1, 138.6, 143.9, 156.1, 156.3. IR ($CHCl_3$): 3336 (ν_{NH}), 1664 (ν_{CO}) cm^{-1}. FAB-MS: 313 $(M + H)^+$. Anal. Calcd for $C_{19}H_{24}N_2O_2$: C, 73.05%; H, 7.74%; N, 8.97%. Found: C, 73.12%; H, 7.69%; N, 8.77%.

General procedure for the preparation of cyclic di-urea derivatives (4)

To a dry benzene (200 mL) was simultaneously added a solution of amine derivative (**11a** or **12**) (5.0 mmol) in dry benzene (200 mL) and a solution of *m*-xylylene diisocyanate (920 mg, 5.0 mmol) in dry benzene (200 mL) over 4 h at room temperature. After the addition was completed, the mixture was allowed to react at room temperature for 18 h. Removal of benzene gave oily residue, which was subjected to column chromatography on silica gel (**4a**: acetonitril:chloroform 1:2, **4b**: ethyl acetate:chloroform 1:4) to give cyclic bis-urea derivatives (**4**) as colorless crystals.

4a: 16% yield. melting point 261–262 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (s, *t*-Bu × 2, 18H), 3.40 (m, CH_2 × 2, 4H), 3.84 (t, CH_2 × 2, 4H, $J = 4.0$ Hz), 3.91 (bs, NH × 2, 2H), 3.96 (s, CH_2 × 2, 4H), 4.14 (d, CH_2 × 2, 4H, $J = 6.0$ Hz), 4.32 (s, NH × 2, 2H), 6.65 (m, Ar–H × 2, 2H), 6.75 (s, Ar–H, 1H), 7.03 (d, Ar–H × 2, 2H, $J = 8.0$ Hz), 7.17–7.21 (m, Ar–H × 5, 5H). ^{13}C-NMR ($CDCl_3$) δ: 31.4, 34.8, 34.9, 39.9, 44.0, 68.1, 109.9, 110.8, 121.8, 123.9, 125.6, 128.3, 129.0, 140.0, 143.9, 155.2, 157.7. IR ($CHCl_3$): 3350 (ν_{NH}), 1635 (ν_{CO}) cm^{-1}. FAB-MS: 587 $(M + H)^+$. Anal. Calcd for $C_{35}H_{46}N_4O_4$: C, 71.64%; H, 7.90%; N, 9.55%. Found: C, 71.55%; H, 7.97%; N, 9.42%.

4b: 12% yield. melting point 240–241 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (s, *t*-Bu × 2, 18H), 3.49 (m, CH_2 × 2, 4H), 4.00 (q, CH_2 × 4, 8H, $J = 5.0$ Hz), 4.17 (d, CH_2 × 4, 4H, $J = 6.0$ Hz), 5.01 (bs, NH × 2, 2H), 5.07 (bs, NH × 2, 2H), 6.62 (d, Ar–H × 2, 2H, $J = 8.0$ Hz), 6.87 (s, Ar–H, 1H), 6.94 (d, Ar–H × 2, 2H, $J = 8.0$ Hz), 7.05 (d, Ar–H × 2, 2H, $J = 2.0$ Hz), 7.10 (dd, Ar–H × 2, 2H, $J = 2.0, 8.0$ Hz), 7.142(t, Ar–H, 1H, $J = 8.0$ Hz). ^{13}C-NMR ($CDCl_3$) δ: 31.2, 34.2, 39.9, 43.2, 68.4, 111.6, 121.7, 121.8, 125.0, 125.3, 128.2, 128.5, 140.1, 144.8, 154.5, 158.4. IR ($CHCl_3$): 3366 (ν_{NH}), 1636 (ν_{CO}) cm^{-1}. FAB-MS: 605 $(M + H)^+$. Anal. Calcd for $C_{34}H_{44}N_4O_4S$: C, 67.52%; H, 7.33%; N, 9.26%. Found: C, 67.56%; H, 7.52%; N, 9.01%.



Scheme 1 Synthesis of urea derivatives. (i) $ClCH_2CN$, K_2CO_3, NaI in dry acetone, reflux, (ii) $LiAlH_4$, in dry THF, reflux, (iii) OCNR (R = Ph or Ts) or *m*-xylylene diisocyanate, in dry benzene, r.t

Job plot [8]

The ^{1}H NMR sample solutions were made of [receptor]/[quaternary ammonium salt] ratios under the condition that [receptor] + [quaternary ammonium salt] = 3.0 mM in $CDCl_3$, and [quaternary ammonium salt] varies from 0 to 3.0 mM in 0.3 mM steps. The experimentally observed parameter is the ^{1}H NMR chemical shift change ($\Delta\delta$) of the urea NH proton of receptor that is sensitive to complex formation. The data were plotted in the form $\Delta\delta \times$ [receptor] $\times 10^3$ versus [receptor]/([receptor] + [quaternary ammonium salt]), and the position of the maximum indicates the stoichiometry of the complex.

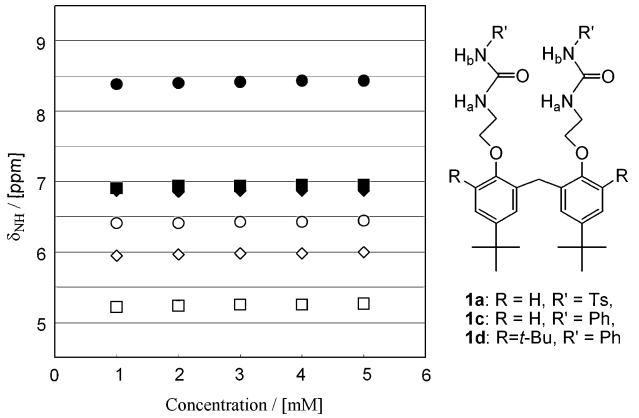


Fig. 2 ^{1}H-NMR Chemical shifts (δ values) of urea NH protons of **1** (3 mM) as a function of concentration in $CDCl_3$. (**1a**: NH_a (◯), NH_b (●), **1c**: NH_a (□), NH_b (■), **1d**: NH_a (◇), NH_b (◆))

Association constant (K_a) [9]

Association constants (K_a) were obtained by ^{1}H-NMR titration experiments, performed directly in the NMR tube using a micropipette to add known amounts (0, 50, 100, 150, 200, 250, 300, 350, 400, 450, 500 µl) of quaternary ammonium salt (**6**) stock solution (concentration = 16.5 mM) in $CDCl_3$ to a solution of receptor (700 µl, concentration = 2.38 mM) in $CDCl_3$. A 1:1 association of receptors and quaternary ammonium salts was previously demonstrated by Job plots, therefore, experimental data were fit to the equation of the 1:1 binding isotherm. All titration experiments were performed in $CDCl_3$ at 297 K and 500 MHz.

Results and discussion

Synthesis of urea derivatives (**1**, **2**, **3**, **4** and **5**)

The diphenylmethane derivatives (**7**), diphenylsulfide derivative (**8**) and biphenyl derivatives (**13**) were prepared according to the previously reported literature [4–7]. The di-urea derivatives (**1**, **2**, **3** and **4**) were prepared as follows (Scheme 1). The reactions of the phenol derivatives (**7**, **8** and **13**) with chloroacetonitrile in the presence of potassium carbonate and sodium iodide in dry acetone at reflux for 12–72 h gave the dinitrile derivatives (**9**, **10** and **14**), which were reduced using lithium aluminum hydride that produced the corresponding diamines (**11**, **12** and **15**) [10]. Finally, the condensation reactions of the amines (**11**, **12** and

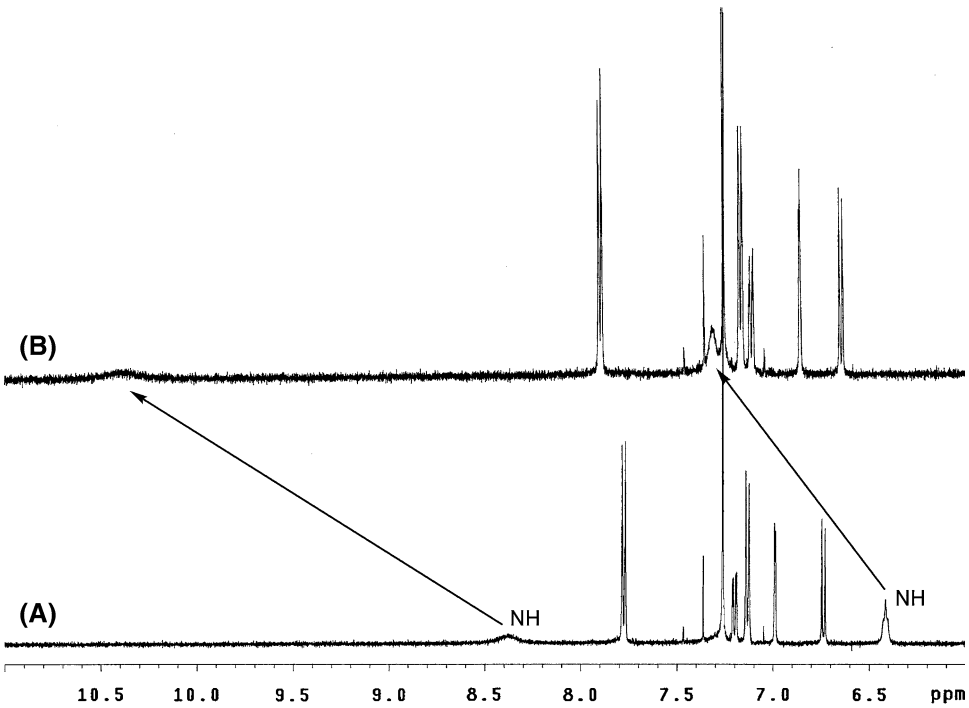


Fig. 3 ^{1}H-NMR Spectra of diphenylmethane-based receptor bearing bis(*p*-toluenesulfonyl urea) units (**1a**) in $CDCl_3$ at 297 K. (**a**) **1a**. (**b**) **1a** + **6a**. ([**1a**] = [**6a**] = 3 mM)

15) with phenyl isocyanate, *p*-toluenesulfonyl isocyanate or *m*-xylylene diisocyanate gave the di-urea derivatives (**1**, **2**, **3** and **4**) [11]. The mono-urea derivatives (**5**) were also prepared by a similar procedure. All compounds were characterized by ^{1}H and ^{13}C NMR, mass and IR spectra, and elemental analysis.

Intermolecular hydrogen bonding

The self-association tendencies of the urea derivatives (**1**–**5**) were evaluated by ^{1}H-NMR analyses in $CDCl_3$. Although the urea derivatives (**1**–**5**) exhibited a downfield shift in the urea NH signals depending on the concentration ($\Delta\delta$ (δ_{NH}(5 mM) − δ_{NH}(1 mM) < 0.08 ppm, excluding cyclic compounds (**4b**) ($\Delta\delta$ = 0.195 ppm), monomer (**5a**) ($\Delta\delta$ = 0.34 ppm) (Fig. 2 and supporting information) [12], the chemical shift difference ($\Delta\delta$) was not as remarkable as that of the self-associated urea derivative previously reported ($\Delta\delta_{NH}$ (δ_{dimer} − $\delta_{monomer}$) = ca. 1.3 ppm) [13]. Therefore, we carried out the following ^{1}H-NMR experiments using the solution of ureas under a 3 mM concentration.

Anion binding ability

The interaction behavior of the ureas (**1**–**5**) and anions (**6**) was investigated by ^{1}H-NMR spectroscopy. A downfield shift of the urea NH protons of **1a** was observed upon the addition of tetra *n*-butyl ammonium chloride (**4a**) to the solution of **1a** in $CDCl_3$, indicating the formation of the complex (**1a**–**4a**) through the intermolecular hydrogen bonding between the urea NH protons and a chloride anion of **4a** (Fig. 3). A similar tendency was also observed when using the other ureas (**1c**, **1d**, **2**, **3**, **4** and **5**) and quaternary ammonium salts (**6**).

As another important finding, the aromatic proton (H_a) resonances of **1a** shifted upfield in the presence of a chloride anion, indicating that the diphenylmethane moiety of **1a** prefers to adopt a *syn* conformation in the complex compared with the free **1a** (Fig. 4) [14]. Therefore, the two urea groups of **1a** in the complex are arranged in the same direction. This observation supported our assumption of the cooperativity of the two urea groups in the anion recognition.

We estimated the stoichiometry of the complexes between the ureas (**1**, **2**, **3**, **4** and **5**) and quaternary ammonium salts (**6**) using the Job plot method [8]. The 1:1

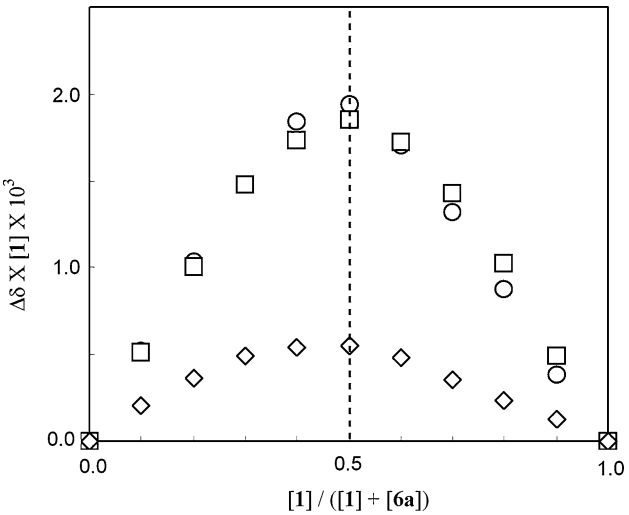


Fig. 5 Job plots of diphenylmethane-bsaed receptors (**1**) with quaternary ammonium chloride (**6a**). (**1a** and **6a**: ◯, **1c** and **6a**: □, **1d** and **6a**: ◇)

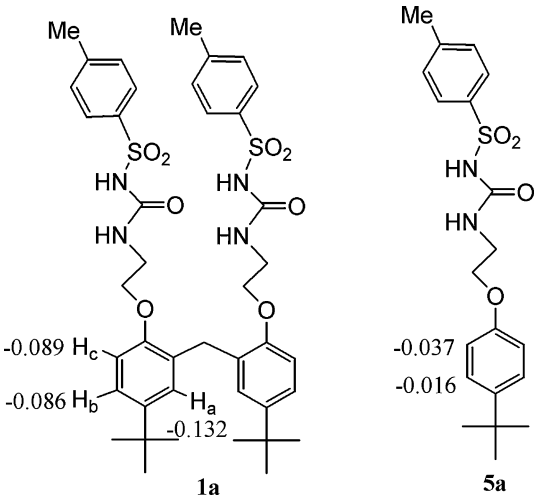


Fig. 4 Induced chemicl shifts [ppm] of **1a** and **5a** in the presence of (n -Bu)$_4$ N$^+$Cl$^-$ at 297 in $CDCl_3$. [**1a**] = [**5a**] = [(n-Bu)$_4$ N$^+$Cl$^-$] = 1.0 mM.− denotes the shift to higher magnetic field

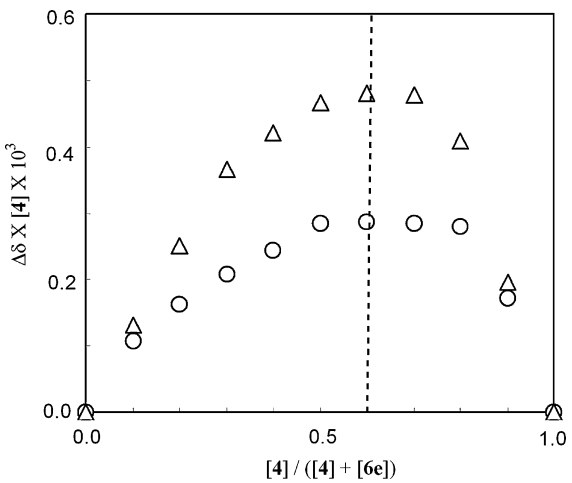


Fig. 6 Job plots of cyclic receptors (**4**) with quaternary ammonium hydrogen sulfate (**6e**). (**4a** and **6e**: Δ, **4b** and **6e**: ◯)

stoichiometry of the complexes was confirmed by the plot that contains a maximum at the mole ratio of 0.5 in these cases (Fig. 5), with the exception of the complex between the cyclic ureas (**4**) with hydrogen sulfate (**6e**), of which the plot contains a maximum at the mole ratio ([**4**]/([**4**] + [**6e**])) of 0.6, indicating a complicated complexation (Fig. 6). The association constants of the ureas (**1**–**5**) toward the various anions (**6**) were determined by a non-linear regression method following the chemical shifts of the urea NH protons by a ^{1}H-NMR titration [9], as shown in Fig. 7, and are summarized in Table 1.

The cooperativity of the two symmetrical halves of the di-ureas (**1**, **2** and **3**) for anion binding was established by checking the binding of the mono-ureas (**5**), which obviously had a lower anion binding ability compared to the di-ureas (**1**, **2** and **3**) under the same experimental conditions.

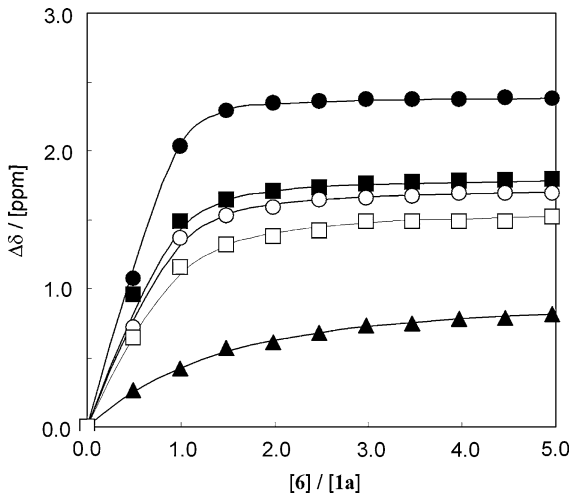


Fig. 7 ^{1}H-NMR titration of **1a** with **6** in $CDCl_3$ at 297 K. Indicated a change in the chemical shift of the NH protons of **1a** as a result of added **6**. Plots are experimental data and curves are calculated by non-linear regression. (Cl^- (**6a**): ●, Br^- (**6b**): ■, I^- (**6c**): ▲, NO_3^- (**6d**): ○, HSO_4^- (**6e**): □)

The anion binding ability of the di-urea derivatives was in the following order: **1a** and **1c**: $Cl^- > Br^- \approx HSO_4^- \approx NO_3^- > I^-$, **2a**: $Cl^- > HSO_4^- > NO_3^- \approx Br^- > I^-$, **3a**: $HSO_4^- > Cl^- > NO_3^- > Br^- > I^-$. Generally, the bis (*p*-touenesulfonyl urea) derivatives (**1a** and **2a**) exhibited an enhanced anion binding ability compared to the bis(phenyl urea) derivatives (**1c**, **1d**, **2c** and **2d**) due to the increasing acidity of the urea NH protons [15], although these receptors (**1a** and **2a**) resembled each other regarding the chloride anion selectivity. The bis(phenyl urea) derivatives (**1d**, **2c**, **2d**, and **3b**) and cyclic compounds (**4a** and **4b**) indicated a low anion affinity and did not show a clear anion selectivity. Interestingly, the diphenylsulfide-based receptors (**3a**) are more effectively bound to the hydrogen sulfate (HSO_4^-) versus the other tested anions. This is probably due to the fact that **3a** is able to provide the better geometry of the two urea groups for hosting hydrogen sulfate by the replacement of the methylene of **1a** by the sulfur.

The diphenylmethane-based receptor (**1a**) is more effectively bound to a chloride anion when compared with analogous compounds (**2**, **3** and **4**) [16]. Considering that a chloride anion is relatively small and has a spherical structure, the most effective hydrogen bonding between the urea groups and a chloride anion is to surround it with two urea groups. The diphenylmethane-based receptor (**1**) is a more flexible structure so that two urea groups are able to permit the optimized arrangement for incorporating a chloride anion [17].

In summary, we synthesized anion receptors based on diphenylmethane (**1**), biphenyl (**2**), diphenylsulfide (**3**) and cyclophane (**4**) bearing urea groups. The diphenylmethane derivative (**1a**) was able to efficiently bind a chloride anion, in a 1:1 fashion upon the multiple hydrogen bond-mediated complexation. Considering a receptor with a

Table 1 Association constants (K_a [M^{-1}] in $CDCl_3$ at 297 K) for 1:1 complexes of urea derivatives (**1**, **2**, **3**, **4** and **5**) and quaternary ammonium salts (**6**) and free energy ($-\Delta G$ [kJ/mol] in $CDCl_3$ at 297 K)

Receptor	Anion[b]				
	Cl^- **6a**	Br^- **6b**	I^- **6c**	NO_3^- **6d**	HSO_4^- **6e**
Association constants (K_a) [M^{-1}][a] (free energy ($-\Delta G$ [kJ/mol]))					
1a	20000 (24.5)	8000 (22.2)	500 (15.3)	6000 (21.5)	3500 (20.2)
1c	5000 (21.0)	1300 (17.7)	250 (13.6)	900 (16.8)	700 (16.2)
1d	280 (13.9)	90 (11.1)	20 (7.4)	300 (14.1)	230 (13.4)
2a	7000 (21.9)	1300 (17.7)	140 (12.2)	2000 (18.8)	4000 (19.0)
2c	340 (14.4)	650 (16.0)	60 (10.1)	520 (15.4)	620 (15.9)
2d	460 (15.1)	1400 (17.9)	180 (12.8)	930 (16.9)	480 (15.2)
3a	5500 (21.3)	1800 (18.5)	140 (12.2)	2700 (19.5)	8000 (22.2)
3b	700 (16.2)	500 (15.3)	20 (7.4)	600 (15.8)	–[c]
4a	250 (13.6)	115 (11.7)	19 (7.3)	70 (10.5)	–[c]
4b	18 (7.1)	13 (6.3)	<10	25 (7.9)	–[c]
5a	700 (16.2)	500 (15.3)	<10	300 (14.1)	450 (15.1)
5b	400 (14.8)	160 (12.5)	40 (9.1)	190 (13.0)	–[c]

[a] Errors were estimated to be 10%

[b] Anions were used as their *n*-Bu_4 N^+ salts

[c] **3b**, **4a**, **4b** and **5b** showed a complicated complexation with **6e**

moderate structural flexibility that could take the appropriate arrangement of the binding site toward the anion guest, the flexible framework of the dipneylmethane moiety could allow the preorganization of a receptor to guide the recognition process of a chloride anion.

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10. Amine derivatives (**11**, **12** and **15**) are instability on the purification process. Therefore, these amines were used to the next step without further purification
11. Although we tried to prepare bis-urea derivatives (**1b** and **2b**) from the reactions of diamine (**11b** or **15b**) with *p*-toluenesulfonyl isocyanate under several reaction conditions, we did not obtain **1b** and **2b** except polymeric materials
12. When the concentration of **1–5** increased from 1 mM to 5 mM, the urea NH signals moved downfield (**1a**: $\Delta\delta$ (δ_{NH}(5 mM) − δ_{NH}(1 mM)) [ppm] = 0.031 (NH_a), 0.057 (NH_b), **1c**: 0.050 (NH_a), 0.056 (NH_b), **1d**: 0.043 (NH_a), 0.006 (NH_b), **2a**: 0.022 (NH_a), 0.025 (NH_b), **2b**: −0.005 (NH_a), −0.004 (NH_b), **2c**: 0.018 (NH_a), 0.074 (NH_b), **2d**: 0.036 (NH_a), 0.073 (NH_b), **3a**: 0.016 (NH_a), 0.023 (NH_b), **3b**: 0.028 (NH_a), 0.034 (NH_b), **4a**: 0.109 (NH_a), 0.076 (NH_b), **4b**: 0.195 (NH_a), 0.125 (NH_b), **5a**: 0.340 (NH_a), 0.004 (NH_b), **5b**: 0.051 (NH_a), 0.081 (NH_a)
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16. Other studies also reported that anion receptors based on rigid framework such as calixarene have the binding constant values of the order of magnitude ($K_a = \sim 10^6$) with chloride anion [2d], which is higher than that of our receptor (**1a**) ($K_a = \sim 10^4$). However **1a** is comparatively high binding constant of chloride in the flexible structural urea-based receptor reported previously ($K_a = \sim 10^3$) [3c]
17. We also investigated about counter cation effect in the anion recognition of diphenylmethane derivative (**1a**) using triethyl benzyl ammonium chloride (TEBACl) and trimethyl benzyl ammonium chloride (TMBACl). The association constants between **1a** and quaternary ammonium salts were 41000 M^{-1} (**1a**-TEBACl) and 10000 M^{-1} (**1a**-TMBACl), respectively. The anion affinity of **1a** was affected by the cation component of quaternary ammonium salts. Considering that quaternary ammonium salts form a tight ion-pair in non-polar solvent such as chloroform, it is interactive for an anion receptor to be away from the distance between the cation and the anion components in quaternary ammonium salt. Therefore, a chloride anion of triethyl benzyl ammonium salt can be strongly interactive with the urea NH protons of **1a** compared with that of trimethyl benzyl ammonium salt