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ORIGINAL ARTICLE

Biaryl-based anion receptors bearing thiourea groups: fluoride anion receptor

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Abstract The synthesis, characterization and binding studies with anions for biaryl-based anion receptors bearing thiourea groups have been described. The results revealed that receptors (**1** and **2**) showed good selectivity and binding affinity for F^-, and among them binaphthyl-based receptor (**1a**) showed the best binding affinity for F^- in comparison to other tested anions (Cl^-, Br^-, I^-, NO_3^-, HSO_4^-, AcO^- and $H_2PO_4^-$). This is probably due to the fact that the moderate rigidity of binaphthyl skeleton in **1a** is able to provide the better geometry of two thiourea groups for incorporating F^- into the binding pocket. The higher basicity of F^- also participated in this selectivity.

Keywords Anion receptor · Biaryl · Thiourea · Fluoride anion

Introduction

Anion sensing and recognition have received increasing recent attention in supramolecular, organic and inorganic chemistry [1–11]. A number of anion receptors have been reported so far which have various functional groups as anion binding sites, including neutral hydrogen bonding donors (for example amide, urea and thiourea) or positively charged functional groups (for example ammonium, guanidium, pyridinium and imidazolium) [12–16]. Neutral anion receptors capable of hydrogen bonding to anions have been extensively studied because hydrogen bonding exerts directional non-covalent interaction with certain anions, which can provide one or more hydrogen bonding sites for selective binding and sensing of certain anions.

Considering that receptors with higher structural dimension tend to exhibit larger binding ability and selectivity toward guest species, one of the strategies used to design receptors which bind a guest anion strongly and selectively is to increase dimensions of their structures in order to arrange the binding sites in an appropriate position for the complexation with a guest anion [17, 18]. Therefore, we conceived on an idea to be used biaryl unit as a backbone of an anion receptor because biaryl skeleton combines moderate rigidity and flexibility [19–21]. This structural property of biaryl unit will be expected to minimize the energy loss by the conformational rearrangement during the complexation process and also provide the suitable binding site toward a guest anion. In this context, we describe here the synthesis and anion binding properties of the receptors based on biaryl unit bearing two thiourea groups as the hydrogen bonding donors (Fig. 1).

Experimental

Melting points were measured by Stuart SMP3 melting point apparatus and were not corrected. ^1H and ^{13}C NMR spectra were measured by Varian INOVA 500 (500 MHz for ^1H, 125 MHz for ^{13}C) and/or Varian Mercury 200 (200 MHz for ^1H, 50 MHz for ^{13}C) spectrophotometers. Tetramethylsilane was used as an internal standard reference. Fab-mass spectra (MS) were collected by JEOL AX-505HA spectrometer using *m*-nitrobenzyl alcohol as a matrix. IR spectra were recorded on FORIBA FT-720 spectrophotometer. UV–vis spectra were recorded on

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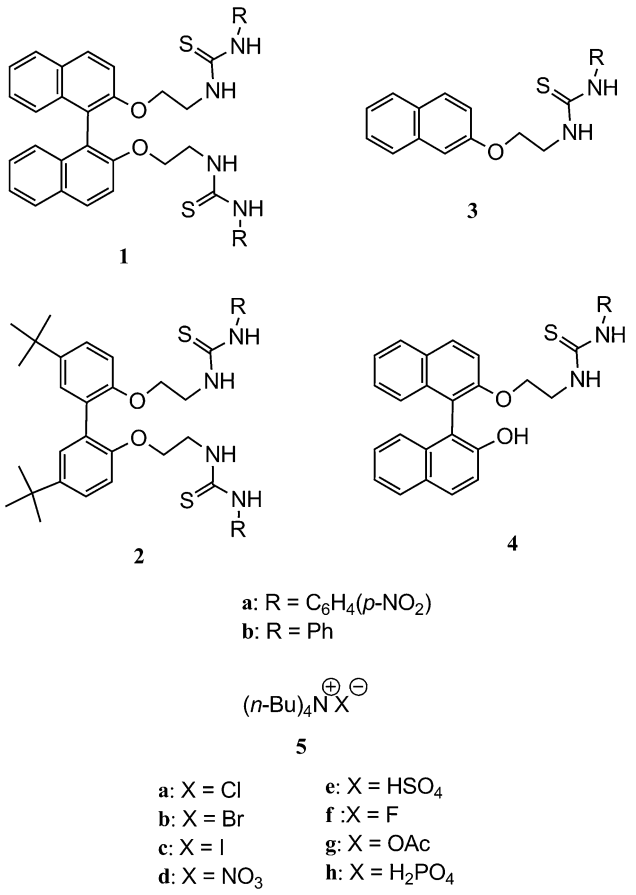


Fig. 1 Thiourea derivatives (**1**–**4**) and quaternary ammonium salts (**5**)

Hitachi U-2020 spectrophotometer. All chemicals were reagent grade and were used without further purification. Chloroacetonitrile, sodium iodide, potassium carbonate, lithium aluminum hydride, *p*-nitrophenyl isothiocyanate, phenyl isothiocyanate, tetra-*n*-butyl ammonium salts (**5a**–**h**) and 2-naphthol (**6**) were purchased from Kanto Chemical Co., Tokyo Kasei Industry and Aldrich. 1,1′-Binaphthyl-2,2′-diol (**7**) [22], 2,2′-cyanomethoxy-1,1′-binaphthyl (**8**) [23], 5,5′-di-*t*-butyl biphenyl-2,2′-diol (**9**) [24], 5,5′-di-*t*-butyl-2,2′-cyanomethoxy-1,1′-biphenyl (**10**) [25] and 2-cyanomethoxy naphthalene (**11**) [26] were prepared according to the literature.

Synthesis of 2-cyanomethoxy-2′-hydroxy-1,1′-binaphthyl (**12**)

A mixture of **7** (0.90 g, 3.15 mmol), chloroacetonitrile (0.20 ml, 3.15 mmol), sodium iodide (0.20 g, 9.24 mmol), potassium carbonate (0.522 g, 3.78 mmol) in dry acetone (100 ml) was refluxed for 3 h. After removal of solvent, the residue was dissolved with chloroform. The solution was washed with water twice and dried over anhydrous sodium sulfate. Removal of solvent gave the amorphous reside, which was subjected to column chromatography on silica gel using hexane/ethyl acetate, 8/1 as an eluent to give **12** (291 mg, 29 %) as colorless crystals accompanying with recovery of **7** (585 mg, 65 %).

12

Mp 162–163 °C. ^{1}H NMR ($CDCl_3$) δ: 4.57 (d, –OC*H*HCN, 1H, J = 16.0 Hz), 4.61 (d, –OCH*H*CN, 1H, J = 16.0 Hz), 4.84 (s, OH, 1H), 7.03 (d, Ar–H, 1H, J = 8.5 Hz), 7.25–7.40 (m, Ar–H, 5H), 7.48 (dd, Ar–H, 1H, J = 6.5, 8.0 Hz), 7.56 (d, Ar–H, 1H, J = 9.0 Hz), 7.88 (d, Ar–H, 1H, J = 8.0 Hz), 7.94 (d, Ar–H, 1H, J = 6.5 Hz), 7.96 (d, Ar–H, 1H, J = 8.0 Hz), 8.12 (d, Ar–H, 1H, J = 9.0 Hz). ^{13}C NMR ($CDCl_3$) δ: 55.3, 113.7, 115.2, 117.7, 119.1, 123.8, 124.5, 125.7, 127.0, 127.9, 128.3, 128.5, 129.2, 130.5, 131.0, 131.6, 133.6, 133.9, 151.3, 153.0. Fab-MS 236 $(M+H)^+$. Anal. calcd for $C_{22}H_{15}NO_2$: C, 81.21 %; H, 4.65 %; N, 4.30 %. Found: C, 81.15 %; H, 4.78 %; N, 4.23 %.

Synthesis of thiourea derivative (**1a**)

A solution of **8** (364 mg, 1.0 mmol) in dry ether (50 ml) was added lithium aluminum hydride (152 mg, 4.0 mmol) at room temperature. After the addition was completed, the mixture was refluxed for 4 h. The reaction mixture was cooled in an ice-bath and wet-benzene was added. The precipitate was removed by filtration. The filtrate was washed with water and the organic layer was dried over anhydrous sodium sulfate. Removal of solvent gave oily residue, which was dissolved with dry chloroform (30 ml). To the solution was added *p*-nitrophenyl isothiocyanate (360 mg, 2.0 mmol) and the mixture was stirred at room temperature for 16 h. Removal of solvent gave oily residue, which was subjected to column chromatography on silica gel using hexane/ethyl acetate, 2/3 as an eluent to give **1a** (586 mg, 80 % yield) as pale yellow crystals. The similar procedure as described above was applied to prepare **1b**, **2**–**4**.

1a

Mp 164–165 °C. ^{1}H NMR ($CDCl_3$) δ: 3.62 (m, –C*H*HN–, 2H), 3.78 (m, –CH*H*N–, 2H), 4.09 (m, –OC*H*H–, 2H), 4.31 (m, –OCH*H*–, 2H), 6.18 (bs, NH, 2H), 7.10 (d, Ar–H, 2H, J = 9.0 Hz), 7.27 (dd, Ar–H, 2H, J = 8.0, 8.5 Hz), 7.33 (d, Ar–H, 4H, J = 9.0 Hz), 7.36 (dd, Ar–H, 2H, J = Hz), 7.40 (d, Ar–H, 2H, J = 9.0 Hz), 7.50 (bs, NH, 2H), 7.83 (d, Ar–H, 2H, J = 8.0 Hz), 7.91 (d, Ar–H, 2H, J = 9.0 Hz), 8.06 (d, Ar–H, 4H, J = 8.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 44.6, 68.8, 116.2, 120.6, 121.6, 124.5, 124.8,

125.1, 127.0, 128.2, 129.7, 130.1, 133.6, 143.7, 153.4, 180.0. Fab-MS 733 $(M+H)^+$. Anal. calcd for $C_{38}H_{32}N_6O_6S_2$: C, 62.28 %; H, 4.40 %; N, 11.47 %, S, 8.75 %. Found: C, 62.09 %; H, 4.65 %; N, 11.25 %; S, 8.55 %.

1b

Mp 146–147 °C. ^{1}H NMR ($CDCl_3$) δ: 3.55 (m, –C*H*HN–, 2H), 3.70 (m, –CH*H*N–, 2H), 4.05 (m, –OC*H*H–, 2H), 4.14 (m, –OCH*H*–, 2H), 5.97 (bs, NH, 2H), 6.93 (m, Ar–H, 2H), 7.01 (d, Ar–H, 2H, $J = 8.5$ Hz), 7.17–7.22 (m, Ar–H, 4H), 7.29–7.37 (m, Ar–H, 3H), 7.85 (d, Ar–H, 2H, $J = 8.0$ Hz), 7.89 (d, Ar–H, 2H, $J = 8.5$ Hz). ^{13}C NMR ($CDCl_3$) δ: 45.2, 68.5, 116.2, 120.5, 124.2, 124.4, 125.1, 126.6, 126.7, 128.1, 129.6, 129.8, 133.7, 136.4, 153.7, 180.6. Fab-MS 642 $(M+H)^+$. Anal. calcd for $C_{38}H_{34}N_4O_2S_2$: C, 71.00 %; H, 5.33 %; N, 8.72 %, S, 9.98 %. Found: C, 70.82 %; H, 5.47 %; N, 8.60 %; S, 9.77 %.

2a

Mp 140–141 °C. ^{1}H NMR ($CDCl_3$) δ:0.1.32 (e, *t*-Bu, 18H), 3.82 (bs, –CH_2N–, 4H), 4.13 (bs, –OCH_2–, 4H), 6.87 (bs, NH 2H), 7.20–7.40 (m, Ar–H, 12H), 8.03 (bs, Ar–H, 2H), 9.00 (bs, NH, 2H). ^{13}C NMR ($CDCl_3$) δ: 31.7, 34.6, 45.0, 67.3, 113.4, 121.9, 125.3, 125.9, 127.7, 129.4, 143.6, 143.9, 145.2, 153.1, 180.3. Fab-MS 745 $(M+H)^+$. Anal. calcd for $C_{38}H_{44}N_6O_6S_2$: C, 61.27 %; H, 5.95 %; N, 11.28 %, S, 8.61 %. Found: C, 61.02 %; H, 6.02 %; N, 11.05 %; S, 8.40 %.

2b

Mp 170–171 °C. ^{1}H NMR ($CDCl_3$) δ: 1.27 (s, *t*-Bu, 18H), 3.81 (bs, –CH_2N–, 4H), 3.99 (bs, –OCH_2–, 4H), 6.30 (bs, NH, 2H), 6.74 (d, Ar–H, 2H, $J = 7.0$ Hz), 7.04–7.32 (m, Ar–H, 14H), 7.60 (bs, NH, 2H). ^{13}C NMR ($CDCl_3$) δ: 31.4, 34.1, 45.0, 67.6, 113.1, 124.3, 125.3, 126.6, 127.8, 128.8, 129.9, 136.4, 144.1, 153.2, 180.6. Fab-MS 655 $(M+H)^+$. Anal. calcd for $C_{38}H_{46}N_4O_2S_2$: C, 69.69 %; H, 7.08 %; N, 8.55 %, S, 9.79 %. Found: C, 69.88 %; H, 6.92 %; N, 8.43 %; S, 9.53 %.

3a

Mp 157–158 °C. ^{1}H NMR ($CDCl_3$) δ: 4.19 (bs, –CH_2N–, 2H), 4.36 (t, –OCH_2–, 2H, $J = 5.0$ Hz), 6.79 (bs, NH, 1H), 7.08 (dd, Ar–H, 1H, $J = 2.0$, 8.5 Hz), 7.17 (d, Ar–H, 1H, $J = 2.0$ Hz), 7.36 (m, Ar–H, 2H), 7.37 (dd, Ar–H, 1H, $J = 7.5$, 8.0 Hz), 7.47 (dd, Ar–H, 1H, $J = 7.5$, 8.0 Hz), 7.73 (d, Ar–H, 1H, $J = 8.5$ Hz), 7.78 (d, Ar–H, 1H, $J = 8.0$ Hz), 7.79 (d, Ar–H, 1H, $J = 8.0$ Hz), 7.90 (bs, NH, 1H), 8.23 (m, Ar–H, 2H). ^{13}C NMR ($CDCl_3$) δ: 43.7, 66.3, 106.9, 118.5, 120.7, 123.9, 124.4, 126.6, 126.8, 127.6, 129.0, 129.5, 134.4, 142.6, 146.1, 156.3, 180.9. Fab-MS 368 $(M+H)^+$. Anal. calcd for $C_{19}H_{17}N_3O_3S$: C, 62.11 %; H, 4.66 %; N, 11.44 %, S, 8.73 %. Found: C, 61.88 %; H, 4.92 %; N, 11.25 %; S, 8.50 %.

3b

Mp 137–138 °C. ^{1}H NMR ($CDCl_3$) δ: 4.15 (dt, –CH_2N–, 2H, $J = 5.0$, 5.5 Hz), 4.30 (t, –OCH_2–, 2H, $J = 5.0$ Hz), 6.57 (bs, NH, 1H), 7.02 (dd, Ar–H, 1H, $J = 2.0$, 9.0 Hz), 7.13 (d, Ar–H, 1H, $J = 2.0$ Hz), 7.18 (d, Ar–H, 2H, $J = 8.0$ Hz), 7.31 (t, Ar–H, 1H, $J = 8.0$ Hz), 7.36 (dd, Ar–H, 1H, $J = 7.5$, 8.0 Hz), 7.41 (t, Ar–H, 2H, $J = 8.0$ Hz), 7.45 (dd, Ar–H, 1H, $J = 6.5$, 8.0 Hz), 7.65 (bs, NH, 1H), 7.72 (d, Ar–H, 1H, $J = 6.5$ Hz), 7.74 (d, Ar–H, 1H, $J = 9.0$ Hz), 7.77 (d, Ar–H, 1H, $J = 7.5$ Hz). ^{13}C NMR ($CDCl_3$) δ: 46.9, 66.4, 107.1, 118.4, 124.1, 125.3, 126.7, 126.9, 127.6, 127.7, 129.2, 129.7, 130.4, 134.5, 135.9, 156.2, 180.8. Fab-MS 322 $(M+H)^+$. Anal. calcd for $C_{19}H_{18}N_2OS$: C, 70.78 %; H, 5.63 %; N, 8.69 %; S, 9.94 %. Found: C, 70.58 %; H, 5.80 %; N, 8.45 %; S, 9.87 %.

4a

Mp 157–158 °C. ^{1}H NMR ($CDCl_3$) δ: 3.75 (bs, –C*H*HN–, 1H), 3.88 (bs, –CH*H*N–, 1H), 4.22 (bs, –OC*H*H–, 1H), 4.33 (bs, –OCH*H*–, 1H), 5.03 (s, OH, 1H), 5.83 (bs, NH, 1H), 7.05 (bs, NH, 1H), 7.09 (d, Ar–H, 1H, $J = 9.0$ Hz), 7.19 (d, Ar–H, 1H, $J = 8.5$ Hz), 7.26 (dd, Ar–H, 1H, $J = 8.0$, 9.0 Hz), 7.28 (d, Ar–H, 1H, $J = 8.0$ Hz), 7.32 (dd, Ar–H, 1H, $J = 8.0$, 8.5 Hz), 7.34 (dd, Ar–H, 1H, $J = 8.0$, 8.5 Hz), 7.37 (m, Ar–H, 2H), 7.43 (dd, Ar–H, 1H, $J = 5.5$, 8.0 Hz), 7.46 (d, Ar–H, 1H, $J = 9.0$ Hz), 7.86 (d, Ar–H, 1H, $J = 8.0$ Hz), 7.88 (d, Ar–H, 1H, $J = 8.5$ Hz), 7.94 (d, Ar–H, 1H, $J = 8.5$ Hz), 8.09 (d, Ar–H, 1H, $J = 9.0$ Hz), 8.15 (m, Ar–H, 2H). ^{13}C NMR ($CDCl_3$) δ: 44.6, 67.9, 115.1, 115.3, 117.6, 122.1, 123.8, 124.8, 124.9, 125.0, 125.1, 125.2, 127.0, 127.8, 128.5, 129.6, 129.7, 128.0, 130.2, 131.6, 133.6, 133.8, 143.7, 144.1, 150.9, 154.5, 180.3. Fab-MS 510 $(M+H)^+$. Anal. calcd for $C_{29}H_{23}N_3O_4S$: C, 68.35 %; H, 4.55 %; N, 8.25 %, S, 6.29 %. Found: C, 68.15 %; H, 4.78 %; N, 8.10 %; S, 6.22 %.

4b

Mp 139–140 °C. ^{1}H NMR ($CDCl_3$) δ: 3.64 (m, –C*H*H–N, 1H), 3.89 (m, –CH*H*–N, 1H), 4.21 (m, O–C*H*H–, 1H), 4.34 (m, O–CH*H*–, 1H), 4.80 (bs, OH, 1H), 6.01 (bs, 1H, NH, 1H), 6.97–7.00 (m, Ar–H, 3H), 7.14 (d, Ar–H, 1H,

$J = 8.0$ Hz), 7.15 (d, Ar–H, 1H, $J = 8.5$ Hz), 7.18 (dd, Ar–H, 1H, $J = 8.0$, 8.5 Hz), 7.22–7.30 (m, Ar–H and NH, 6H), 7.40 (dd, Ar–H, 1H, $J = 8.0$, 8.5 Hz), 7.46 (d, Ar–H, 1H, $J = 9.0$ Hz), 7.82 (d, Ar–H, 1H, $J = 9.0$ Hz), 7.83 (d, Ar–H, 1H, $J = 8.5$ Hz), 7.92 (d, Ar–H, 1H, $J = 8.2$ Hz), 8.06 (d, Ar–H, 1H, $J = 9.0$ Hz). ^{13}C NMR ($CDCl_3$) δ: 45.2, 68.0, 115.1, 115.2, 116.4, 117.5, 123.5, 124.6, 124.8, 124.8, 125.1, 126.7, 127.0, 127.5, 128.2, 128.3, 129.1, 129.9, 130.0, 130.0, 131.3, 133.7, 134.0, 136.3, 151.0, 154.8, 180.9. Fab-MS 465 $(M+H)^+$. Anal. calcd for $C_{29}H_{24}N_2O_2S$: C, 74.97 %; H, 5.21 %; N, 6.03 %, S, 6.90 %. Found: C, 74.77 %; H, 5.40 %; N, 5.98 %; S, 6.68 %.

Results and discussion

Synthesis of receptors

1,1′-Binaphthyl-2,2′-diol (**7**) was prepared by oxidative coupling reaction of 2-naphthol (**6**) with $FeCl_3 \cdot 6H_2O$ in the solid state at 50 °C for 3 h with 90 % yield. The reaction of **7** with chloroacetonitrile in the presence of potassium carbonate and sodium iodide in dry acetone at reflux for 14 h gave 2,2′-bis(cyanomethoxy)-1,1′-binaphthyl (**8**) in 49 % yield. Reduction of **8** was achieved by using lithium aluminum hydride and the condensation reactions of the reductant with *p*-nitrophenyl isothiocyanate gave di-thiourea derivative (**1a**) in 28 % yield. The di-thiourea derivatives (**1b** and **2**) and mono-thiourea derivatives (**3** and **4**) was also prepared by the similar procedure as described for **1a** in 15 % (**1b**), 43 % (**2a**), 20 % (**2b**), 31 % (**3a**), 66 % (**3b**), 33 % (**4a**) and 31 % (**4b**) yields, respectively (Scheme 1). All products (**1–4**) were characterized by ^{1}H and ^{13}C NMR, Fab-MS and elemental analysis.

Intermolecular hydrogen bonding

The self-association tendency of the di-thiourea derivative (**1a**) was evaluated using ^{1}H NMR analysis in $CDCl_3$. The NH signals of thiourea derivative (**1a**) were observed at δ_{NH} 5.0–7.8 ppm at a 1 mM concentration. When the concentration of 1 mM increased to 5 mM, the NH signals moved slightly downfield (Table S1). A similar tendency was also observed for the NH protons of other mono- and di-thiourea derivatives (**1b**, **2–4**). It is postulated that the intermolecular hydrogen bonding hardly occurs based on the slight change in the NH proton chemical shifts of the thiourea derivatives (**1–4**) in this range of concentrations [27]. Therefore, we carried out the following NMR experiments using a solution of the thiourea derivatives (**1–4**) under a 3 mM concentration.

Interaction of thioureas with anions

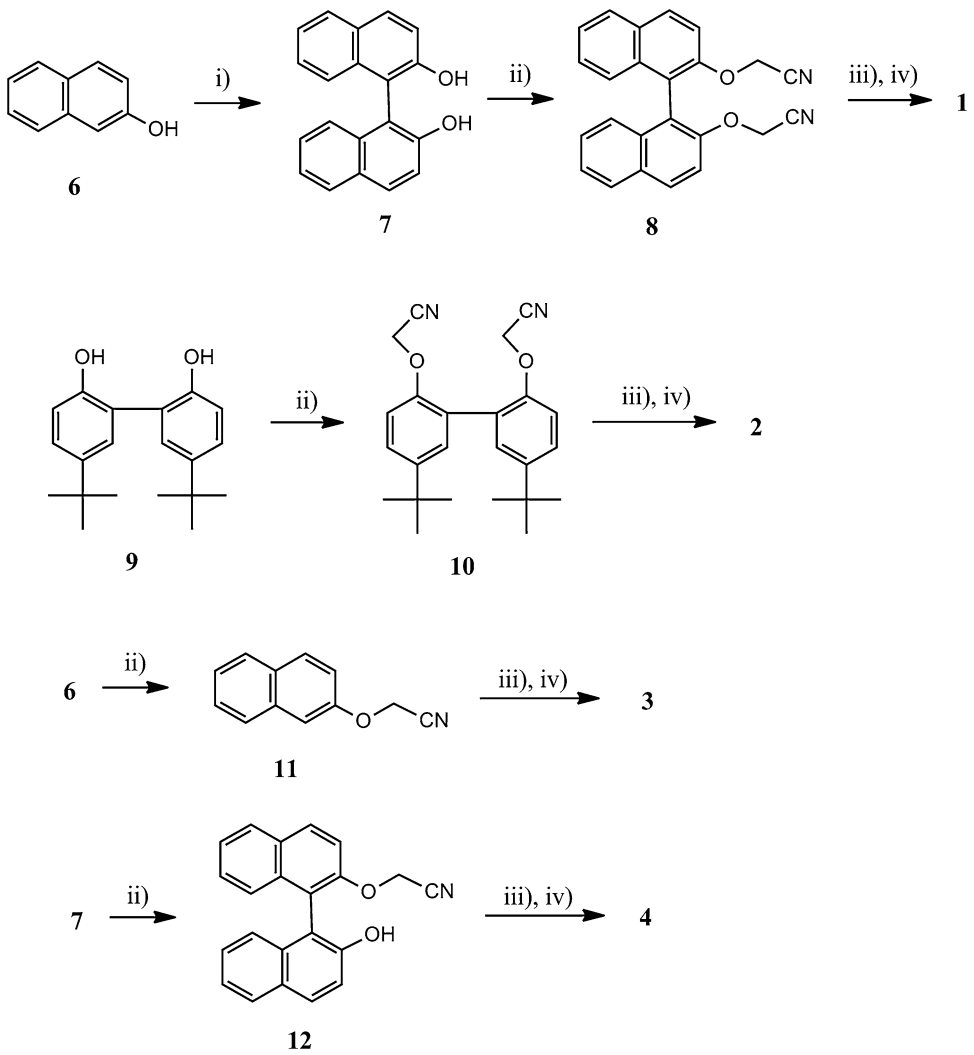
The interaction behavior of di-thioureas (**1**) and anions (**5**) was investigated by ^{1}H NMR spectroscopy. A downfield shift of the di-thiourea NH protons ($\Delta\delta_{NH} = 1.83$ (NH_a), 3.25 (NH_b) ppm) of **1a** was observed upon the addition of tetra-*n*-butyl ammonium chloride (**5a**) to the solution of **1a** in $CDCl_3$ ([**1a**] = [**5a**] = 3 mM), indicating the formation of the complex (**1a–5a**) through the intermolecular hydrogen bonding between the thiourea NH protons and Cl^- (Fig. 2). A similar tendency was also observed using other receptors (**1b**, **2–4**) and quaternary ammonium salts (**5a–e**). Interestingly, the OH proton of **4** also fairly shifted downfield ($\Delta\delta_{OH} = 3.70$ ppm [**4a**], 1.85 ppm [**4b**]) (Fig. 3), indicating the participation of the OH proton in the formation of the complexes (**4**, **5a**) [28–32]. In contrast, the NH proton signals of receptors (**1–4**) became significantly broad upon the addition of basic anions (F^- [**5f**], AcO^- [**5g**] and $H_2PO_4^-$ [**5h**]).

The resonances of the *n*-butyl groups of quaternary ammonium salts (**5a**) shifted upfield in the presence of the thiourea derivatives (**1a**). The induced chemical shift changes ($\Delta\delta$) in the *n*-butyl groups of **5a** increased due to the protons near the cation moiety (N^+) of the quaternary ammonium component (Fig. S1). This order ($\Delta\delta_H^1 > \Delta\delta_H^2 > \Delta\delta_H^3 > \Delta\delta_H^4$) is similar to the acidity of the alkyl protons. Therefore, it is likely that the upfield shift of the *n*-butyl groups is the main cause of the cation–π interaction between the quaternary ammonium part of **5** and the naphthyl moieties of the receptors as the π-component [33, 34].

We also found that the thiourea NH protons of **1–4** ($\Delta\delta/\Delta T$ [ppb/K] = 3.5–10.9) displayed a temperature dependence in the presence of **5a** (Fig. S2). Contrary to this, there was slight change in the thiourea NH protons ($\Delta\delta/\Delta T$ [ppb/K] = 0.8–3.5) in the absence of an anion (Fig. S3). The OH protons of the mono-thiourea derivatives (**4**) were more sensitive to the temperature and showed a significant change in the presence of **5a** ($\Delta\delta/\Delta T$ [ppb/K] = 18.8 [**4a**], 19.3 [**4b**]), while the temperature dependencies ($\Delta\delta/\Delta T$) of **4** were 2.3 (**4a**) and 0.8 (**4b**) (ppb/K) in the absence of an anion (Fig. S4). These temperature dependencies suggest that the NH and OH protons in the presence of **5a** equilibrate between the hydrogen-bonded and non-hydrogen-bonded states [35–37], and provide further support that the NH and OH protons of the receptors are the anion binding sites.

Anion binding properties of thiourea derivatives (1–4)

We estimated the stoichiometry of the complexes between the thioureas (**1–4**) and quaternary ammonium salts (**5**) using the Job plot method [38]. The 1:1 stoichiometry of



Scheme 1 Synthesis of thiourea derivatives (**1–4**). (i) $FeCl_3$, solvent free, 50 , 4 h, (ii) $ClCH_2CN$, K_2CO_3, NaI, in dry acetone, reflux, (iii) $LiAlH_4$, in dry THF, reflux, (iv) $SCNC_6H_4(p\text{-}NO_2)$ or SCNPh in dry benzene, rt

the complexes was confirmed by a plot that contains a maximum at the mole ratio of 0.5 in these cases (Fig. S5). The association constants (K_a) of the thioureas (**1–4**) toward the various anions (**5a–e**) were determined by a nonlinear regression method following the chemical shifts of the NH protons of the thiourea moiety by ^{1}H NMR titration (Figs. S6–S11) [39, 40], and were summarized in Table 1.

Generally, the *p*-nitrophenyl thiourea derivatives (**1a–4a**) exhibited an enhanced anion binding ability compared to the corresponding phenyl thiourea derivatives (**1b–4b**) due to the increasing acidity of the *p*-nitrophenyl thiourea NH protons, although these receptors (**1–4**) resembled each other in anion selectivity ($Cl^- > Br^- \approx HSO_4^- \approx NO_3^- > I^-$). The cooperativity of the two symmetrical halves of the di-thiourea receptors (**1**) for anion binding was established by comparing the binding of the mono-thiourea receptors (**3**), which had an obviously lower anion binding ability compared to **1** under the same experimental conditions. Interestingly, the mono-thiourea receptors (**4**) based on binaphthyl exhibited a higher selectivity toward Cl^-. It is well known that the phenolic OH exhibits a high affinity for Cl^- [28–32]. Therefore, the observed chloride anion selectivity will be attributed to the cooperative effect of the hydroxyl group in the formation of the complex between **4** and Cl^-. As mentioned above, this was clearly established from the ^{1}H NMR titration experiments in $CDCl_3$ in which a substantial shift in the resonance for the hydroxyl group was observed concomitant with the expected thiourea NH chemical shift migration upon the addition of anions.

As mentioned above, it is difficult to obtain the binding ability of the thiourea derivatives (**1–4**) toward strong basic anion species (F-, AcO^- and $H_2PO_4^-$) by ^{1}H NMR spectroscopy due to the exclusively broadening of the thiourea NH protons upon the addition of the anions. Therefore, we studied the interaction between basic anions and thiourea derivatives (**1–4**) by using UV–vis spectroscopy. Figure 4 shows the anion-induced UV–vis spectral changes of the chloroform solution of **1a**. Upon addition of F^-, the

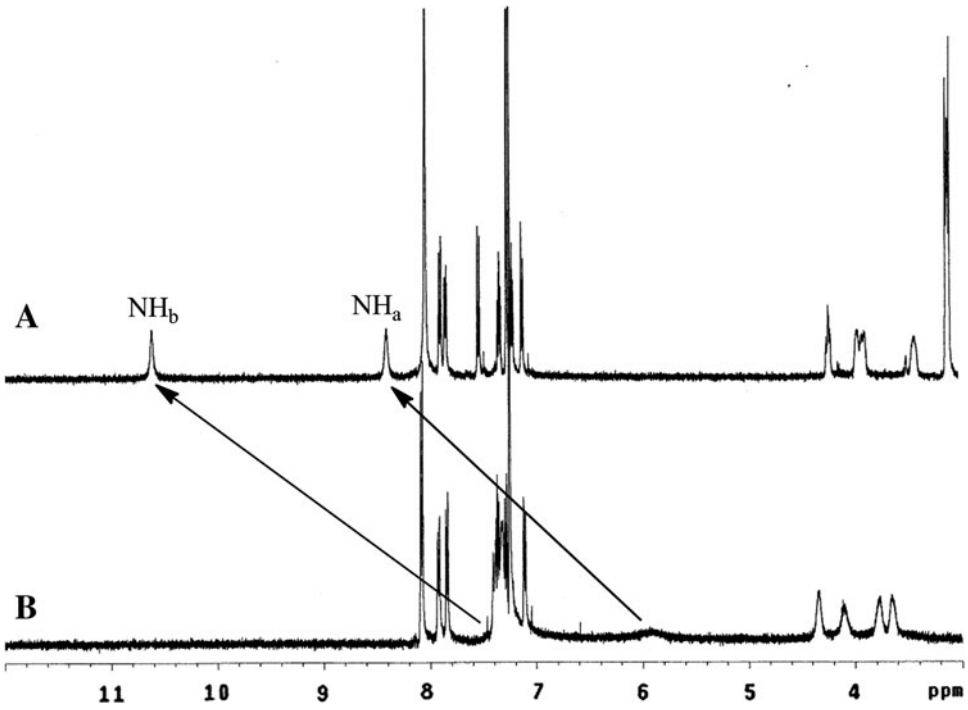


Fig. 2 Partial ^{1}H NMR spectra of **1a** in $CDCl_3$ at 297 K. (**A**) **1a** + **5a**, (**B**) **1a** ([**1a**] = [**5a**] = 3.0 mM)

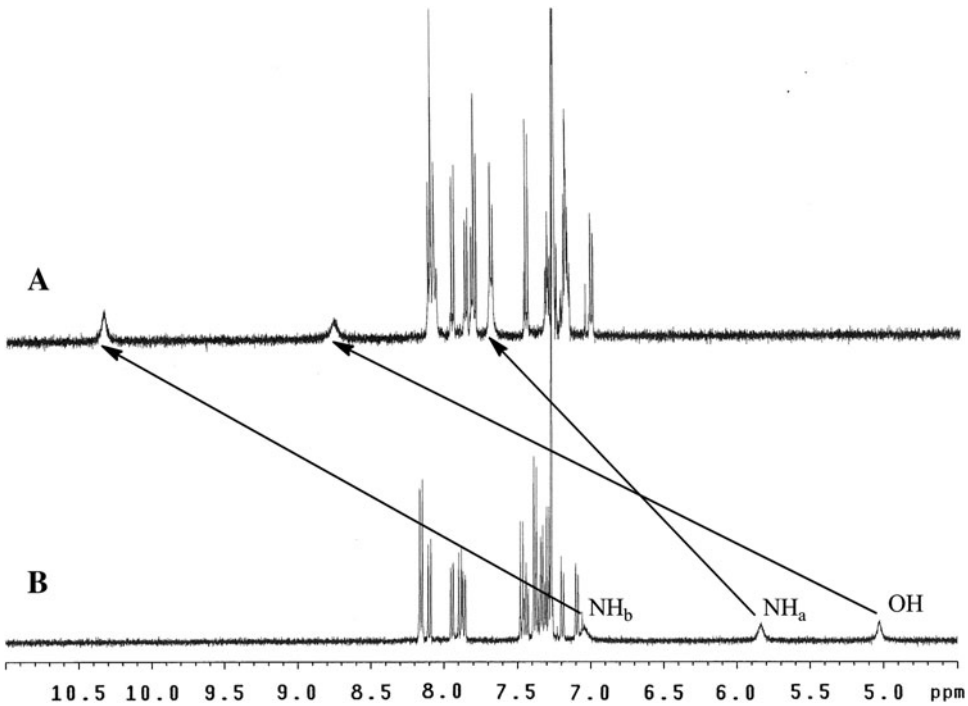


Fig. 3 Partial ^{1}H NMR spectra of **4a** in $CDCl_3$ at 297 K. (**A**) **4a** + **5a**, (**B**) **4a** ([**4a**] = [**5a**] = 3.0 mM)

intensity of the absorption band of **1a** at 333 nm decreased, while the new red-shifted absorption band at around 365 nm appeared. At this time, the presence of a well-defined isosbestic points at 341 and 260 nm was observed. Similar spectral changes were also observed upon addition of AcO^- and $H_2PO_4^-$ (Figs. S12, S13). The observed red-shifted absorption band indicates the formation of the complex between **1a** and the anions (**5e–g**) through the hydrogen bonding. [41, 42]. The association constants (K_a) between the receptors (**1a–3a)** and basic anions (F^-, AcO^- and $H_2PO_4^-$) were obtained by UV–vis titration experiments in $CHCl_3$ (Figs. S14–S19) [39, 40, 43] and the results were summarized in Table 2. Biaryl-based receptors (**1a**, **2a**) were shown in higher selectivity and affinity for F^- in comparison with other basic anions (AcO^- and $H_2PO_4^-$). This selectivity will be attributed to fit the size

Table 1 Logarithms of the association constants (log K_a [M^{-1}] in $CDCl_3$ at 297 K) for 1:1 complexes of thiourea derivatives (**1**–**4**) and quaternary ammonium salts (**5**) and free energy ($-\Delta G$ [kJ/mol] in $CDCl_3$ at 297 K), as evaluated by ^{1}H NMR titration experiments

Log K_a^a (free energy ($-\Delta G$ [kJ/mol]))					
Receptors	Anions[b]				
	Cl^- (**5a**)	Br^- (**5b**)	I^- (**5c**)	NO_3^- (**5d**)	HSO_4^- (**5e**)
1a	4.78 (27.2)	4.32 (24.6)	3.15 (17.9)	4.15 (23.6)	4.30 (24.5)
1b	2.06 (11.7)	1.49 (8.5)	1.17 (6.7)	1.45 (8.2)	1.60 (9.1)
2a	4.46[c] (25.5)	3.97[c] (22.6)	3.04[c] (17.4)	3.97[c] (22.6)	4.18[c] (23.8)
2b	1.76 (10.0)	1.40 (8.0)	<1	1.78 (10.1)	2.40 (13.6)
3a	–[d]	3.32 (19.0)	2.86 (16.3)	3.43 (19.6)	3.15 (17.9)
3b	1.30 (7.4)	1.00 (5.7)	1.30 (7.4)	1.20 (6.8)	1.97 (13.0)
4a	3.90 (22.2)	3.27 (18.6)	2.30 (13.1)	3.00 (17.1)	2.95 (16.8)
4b	2.45 (14.0)	1.70 (9.7)	1.30 (7.4)	1.43 (8.1)	1.54 (8.8)

[a] Errors were estimated to be 10 %

[b] Anions were used as their n-Bu_4N^+ salts

[c] $CDCl_3$/DMSO (95/5, v/v) was used as a solvent due to the low solubility of **2a** in $CDCl_3$

[d] The data does not fit satisfactorily to a 1:1 binding model

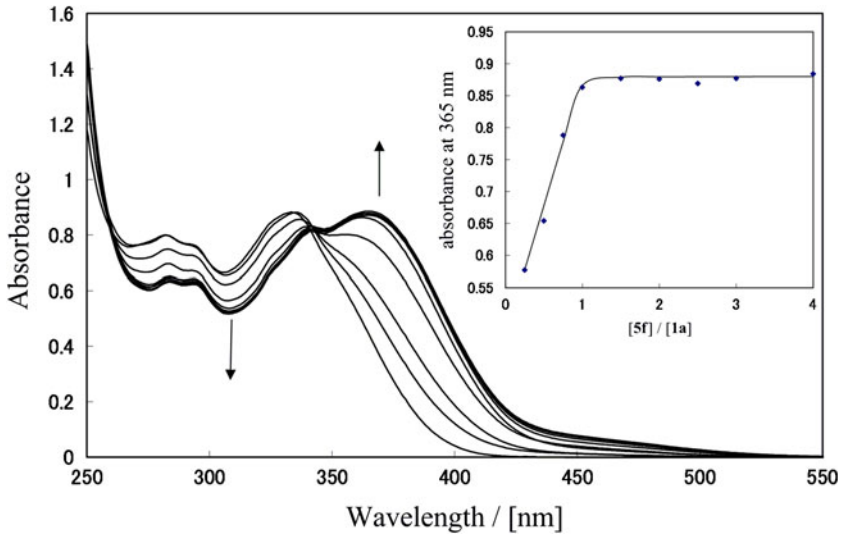


Fig. 4 Changes in UV–vis spectral absorption of **1a** (3.0×10^{-5} mM) upon addition of n-Bu_4N^+ F^- (**5f**) in $CHCI_3$ at 297 K. *Inset* absorbance at 365 nm versus number of mole equivalents of **5f** added

and shape of F^- that is incorporated into the binding pocket, which was constructed from two thiourea groups. The higher basicity of fluoride anion is also considered to participate in this selectivity. Binaphthyl-based receptor (**1a**) is more effectively bound to F^- compared to biphenyl-based receptors (**2a**). This is probably due to the fact that the moderate rigidity of binaphthyl skeleton in **1a** is able to provide the better geometry of two thiourea groups for incorporating F^- into the binding pocket.

A density functional theory (DFT) by B3LYP/6-31G(d,p) level theory has been applied to elucidate the structure of the complex between F^- and binaphthyl-based receptor (**1**) [44–47]. In the optimized structure of the complex (**1**–F^-), **1** incorporated F^- into a suitable binding site, which was constructed by the two thiourea groups. It is noteworthy that the two thiourea groups of **1** in the complex are perpendicular to each other (Fig. 5). The obtained four NH···F^- distances (1.63–1.71 A) are reasonable values as hydrogen bonding distances [48]. We also calculated the structure of the complex between F^- and two thioureas by DFT method (B3LYP/6-31G(d,p) level) and obtained the optimized structure, which has a great resemblance to the optimized structure of the complex (**1**–F^-) (Fig. 6). This result suggests that binaphthyl-based receptor (**1**) bearing two thiourea groups through oxyethylene linker (–OCH_2CH_2–) provide the excellent binding site for F^-.

In summary, we herein described the anion recognition of bis(p-nitrophenyl thiourea) derivative (**1a**) based on

Table 2 Logarithms of the association constants (log K_a [M^{-1}] in $CHCl_3$ at 297 K) for 1:1 complexes of thiourea derivatives (**1–3**) and quaternary ammonium salts (**5f–h**) and free energy ($-\Delta G$ [kJ/mol] in $CHCl_3$ at 297 K), as evaluated by UV–vis titration

Log K_a^a (free energy ($-\Delta G$ [kJ/mol]))			
Anions[b]	Receptors		
	1a	**2a**	**3a**
F^- (**5f**)	7.30 (41.7)	5.90 (33.7)	–[c]
AcO^- (**5g**)	5.85 (33.3)	5.48 (31.2)	4.41 (25.2)
$H_2PO_4^-$ (**5h**)	4.85 (27.6)	5.00 (28.5)	4.25 (24.3)

[a] Errors were estimated to be 10 %

[b] Anions were used as their n-Bu_4N^+ salts

[c] The data does not fit satisfactorily to a 1:1 binding model

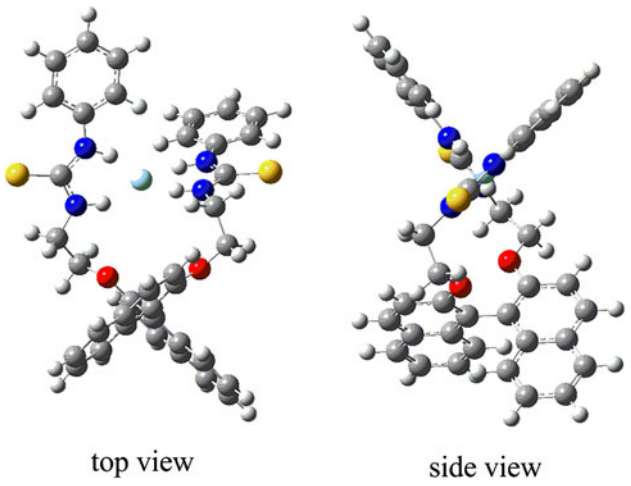


Fig. 5 Optimized geometries of the complex of di-thiourea derivative based on binaphthyl (**1**) with F^- at RB3LYP/6-31G(d,p) level theory

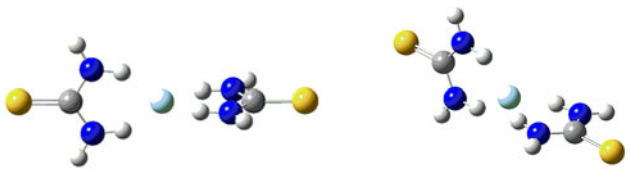


Fig. 6 Optimized geometries of the complex of two thioureas with F^- at RB3LYP/6-31G(d,p) level theory

binaphthyl, which displayed the higher affinity and selectivity toward F^- in comparison to other tested anions (Cl^-, Br^-, I^-, NO_3^-, HSO_4^-, AcO^- and $H_2PO_4^-$). This preference will be attributed to the fitness of size and shape of F^- toward binding pocket of **1a**, which was constructed from two thiourea groups. Further functionalizations of binaphthyl-based receptors (**1**) might provide promising candidates for various applications, such as an asymmetric anion receptor [49] and a hydrogen bonding organocatalyst [50].

References

1. Seel, C., de Mendoza, J., Reetz, M.T.: In: Atwood, J.L., Davies, J.E., MacNicol, D.D., Vogtle, F. (eds.) Comprehensive Supramolecular Chemistry, vol. 2, pp. 519–562. Elsevier Science Ltd., Oxford (1996)
2. Schmidtchen, F.P., Berger, M.: Artificial organic host molecules for anions. Chem. Rev. **97**, 1609–1646 (1997)
3. Gale, P.A.: Anion and ion-pair receptor chemistry: highlights from 2000 and 2001. Coord. Chem. Rev. **240**, 191–221 (2003)
4. Davis, A.P.: Anion binding and transport by steroid-based receptors. Coord. Chem. Rev. **250**, 2939–2951 (2006)
5. Gale, P.A., Quesada, R.: Anion coordination and anion-templated assembly: highlights from 2002 to 2004. Coord. Chem. Rev. **250**, 3219–3244 (2006)
6. Katayev, E.A., Ustynyuk, Y.A., Sessler, J.L.: Receptors for tetrahedral oxyanions. Coord. Chem. Rev. **250**, 3004–3037 (2006)
7. Gale, P.A., Garcia-Garrido, S.E., Garric, J.: Anion receptors based on organic frameworks: highlights from 2005 and 2006. Chem. Soc. Rev. **37**, 151–190 (2008)
8. Caltagirone, C., Gale, P.A.: Anion receptor chemistry: highlights from 2007. Chem. Soc. Rev. **38**, 520–563 (2009)
9. Gale, P.A.: Anion receptor chemistry: highlights from 2008 and 2009. Chem. Soc. Rev. **39**, 3746–3771 (2010)
10. Duke, R.M., Veale, E.B., Pfeffer, F.M., Kruger, P.E., Gunnlaugsson, T.: Colorimetric and fluorescent anion sensors: an overview of recent developments in the use of 1,8-naphthalimide-based chemosensors. Chem. Soc. Rev. **39**, 3936–3953 (2010)
11. Wenzel, M., Hiscock, J.R., Gale, P.A.: Anion receptor chemistry: highlights from 2010. Chem. Soc. Rev. **41**, 480–520 (2012)
12. Li, A.-F., Wang, J.-H., Wang, F., Jiang, Y.-B.: Anion complexation and sensing using modified urea and thiourea-based receptors. Chem. Soc. Rev. **39**, 3729–3745 (2010)
13. Amendola, V., Fabbrizzi, L., Mosca, L.: Anion recognition by hydrogen bonding: urea-based receptors. Chem. Soc. Rev. **39**, 3889–3915 (2010)
14. Kondo, S., Nagamine, M., Karasawa, S., Ishihara, M., Unno, M., Yano, Y.: Anion recognition by 2,2′-binaphthalene derivatives bearing urea and thiourea groups at 8- and 8′-positions by UV–vis and fluorescence spectroscopies. Tetrahedron **67**, 943–950 (2011)
15. García-España, E., Díaz, P., Llinares, J.M., Bianchi, A.: Anion coordination chemistry in aqueous solution of polyammonium receptors. Coord. Chem. Rev. **250**, 2952–2986 (2006)
16. Schmuck, C.: How to improve guanidinium cations for oxoanion binding in aqueous solution?: The design of artificial peptide receptors. Coord. Chem. Rev. **250**, 3053–3067 (2006)
17. Dudic, M., Lhotak, P., Stibor, I., Lang, K., Proskova, P.: Calix[4]arene–porphyrin conjugates as versatile molecular receptors for anions. Org. Lett. **5**, 149–152 (2003)
18. Frontera, A., Morey, J., Oliver, A., Pina, M.N., Quinonero, D., Costa, A., Ballester, P., Deya, P.M., Anslyn, E.V.: Rational design, synthesis, and application of a new receptor for the molecular recognition of tricarboxylate salts in aqueous media. J. Org. Chem. **71**, 7185–7195 (2006)
19. McFarland, S.A., Finney, N.S.: Fluorescent chemosensors based on conformational restriction of a biaryl fluorophore. J. Am. Chem. Soc. **123**, 1260–1261 (2001)
20. Costero, A.M., Andreu, R., Monrabal, E., Martinez-Manez, R., Sancenon, F., Soto, J.: 4,4′-Bis(dimethylamino)biphenyl containing binding sites. A new fluorescent subunit for cation sensing. J. Chem. Soc. Dalton Trans. 1769–1775 (2002). doi:10.1039/B108300G
21. Albrecht, M., Zauner, J., Burgert, R., Rottele, H., Frohlich, R.: Synthesis of tweezer-type receptors for the recognition of anions: observation of an additive effect of hydrogen bonds on nitrate binding. Mater. Sci. Eng. **C18**, 185–190 (2001)

22. Toda, F., Tanaka, K., Iwata, S.: Oxidative coupling reactions of phenols with $FeCl_3$ in the solid state. J. Org. Chem. **54**, 3007–3009 (1989)
23. Puts, R.D., Chao, J., Sogah, D.Y.: Novel chiral biaryl bis(oxazolines). Synthesis, 431–438 (1997)
24. Yamato, T., Hasegawa, K., Saruwatari, Y., Doamekpor, L.K.: Novel spherand-type calixarenes—synthesis, conformational studies and isomer separation. Chem. Ber. **126**, 1435–1439 (1993)
25. Higuchi, S., Sato, T., Ito, K.: Diphentylmethane-based anion receptors bearing bis(*p*-toluenesulfonyl urea) groups. J. Incl. Phenom. Macrocycl. Chem. **62**, 215–222 (2008)
26. Barkin, J.L., Faust Jr., M.D., Trenkle, W.C.: Cytosine analogs from substituted acetonitriles via Thorpe condensation. Org. Lett. **5**, 3333–3335 (2003)
27. Tobe, Y., Sasaki, S.-I., Mizuno, M., Hirose, K., Naemura, K.: Novel self-assembly of *m*-xylylene type dithioureas by head-to-tail hydrogen bonding. J. Org. Chem. **63**, 7481–7489 (1998)
28. Ito, K., Miki, H., Ohba, Y.: Interaction between acyclic phenol–formaldehyde oligomers and quaternary ammonium ions. Yakugaku Zasshi **122**, 413–417 (2002)
29. Smith, D.K.: Rapid NMR screening of chloride receptors: uncovering catechol as a useful anion binding motief. Org. Biomol. Chem. **1**, 3874–3885 (2003)
30. Ito, K., Nagase, K., Morohashi, N., Ohba, Y.: Interaction between quaternary ammonium ions and dideptides: positive anion allosteric effect. Chem. Pharm. Bull. **53**, 90–94 (2005)
31. Winstanley, K.J., Sayer, A.M., Smith, K.D.: Anion binding by catechols an NMR, optical and electrochemical study. Org. Biomol. Chem. **4**, 1760–1767 (2007)
32. Winstanley, K.J., Smith, D.K.: *Ortho*-substituted catechol derivatives: the effect of intramolecular hydrogen-bonding pathways on chloride anion recognition. J. Org. Chem. **72**, 2803–2815 (2007)
33. Nishio, M.: Introduction of Intermolecular Force in Organic Chemistry. Kodansha, Tokyo (2000)
34. Ito, K., Noike, M., Kida, A., Ohba, Y.: Syntheses of chiral homoazacalix[4]arenes incorporating amino acid residues: molecular recognition for racemic quaternary ammonium ions. J. Org. Chem. **67**, 7519–7522 (2002)
35. Nowick, J.S., Pairish, M., Lee, I.Q., Holmes, D.L., Ziller, J.W.: An extended β-strand mimic for a larger artificial β-sheet. J. Am. Chem. Soc. **119**, 5413–5424 (1997)
36. Baxter, N.J., Williamson, M.P.: Temperature dependence of ^1H chemical shifts in proteins. J. Biomol. NMR **9**, 359–369 (1997)
37. Nishiki, M., Oi, W., Ito, K.: Anion binding properties of indolylmethanes. J. Incl. Phenom. Macrocycl. Chem. **61**, 61–69 (2008)
38. Ogoshi, H., Hayashi, T.: Bioorganic chemistry. In: Iguchi, H. (ed.) Encyclopedia of Experimental Chemistry, vol. 27, 4th edn, pp. 19–25. Maruzen Co., Ltd., Tokyo (1991)
39. Hirose, K.: A practical guide for the determination of binding constants. J. Incl. Phenom. Macrocycl. Chem. **39**, 193–209 (2001)
40. Hirose, K.: Determination of binding constants. In: Schalley, C.A. (ed.) Analytical Methods in Supramolecular Chemistry, pp. 17–54. Wiley-VCH, Weinheim (2007)
41. Jennings, A.R., Son, D.Y.: Efficient synthesis and anion recognition of a colorimetric preorganized tripodal thiourea compound. Tetrahedron Lett. **53**, 2181–2184 (2012)
42. Perez-Casas, C., Hopfl, H., Yatsimirsky, A.K.: Structures of urea/thiourea 1,3-disubstituted thia[4]calixarenes and corresponding monofunctional receptors and their anion recognition properties. J. Incl. Phenom. Macrocycl. Chem. **68**, 387–398 (2010)
43. Xie, H., Yi, S., Wu, S.: Study on host–guest complexation of anions based on tri-podal naphthylthiourea derivatives. J. Chem. Soc. Perkin Trans. **2**, 2751–2754 (1999)
44. Friscg, M.J., Trucks, G.W., Schlegel, H.B., Scuseria, G.E., Robb, M.A., Cheeseman, J.R., Scalmani, M., Barone, V., Mennucci, B., Petersson, G.A., Nakatsuji, H., Caricato, M., Li, X., Hratchian, H.P., Izmaylov, A.F., Bloino, J., Zheng, G., Sonnenberg, J.L., Hada, M., Ehara, M., Toyota, K., Fukuda, R., Hasegawa, J., Ishida, M., Nakajima, T., Honda, Y., Kitao, O., Nakai, H., Vreven, T., Montgomery Jr., J.A., Peralta, J.E., Ogliaro, F., Bearpark, M., Heyd, J.J., Brothers, E., Kudin, K.N., Staroverov, V.N., Keith, T., Kobayashi, R., Normand, J., Raghavachari, K., Rendell, A., Burant, J.C., Iyenger, S.S., Tomasi, J., Cossi, M., Rega, N., Millam, J.M., Klene, M., Knox, J.E., Cross, J.B., Bakken, V., Adamo, C., Jaramillo, J., Gomperts, R., Stratmann, R.E., Yazyev, O., Austin, A.J., Cammi, R., Pomelli, C., Ochterski, J.W., Martin, R.L., Morokuma, K., Zakrzewski, V.G., Voth, G.A., Salvador, P., Dannenberg, J.J., Dapprich, S., Daniels, A.D., Farkas, O., Foresman, J.B., Ortiz, J.V., Cioslowski, J., Fox, D.J.: Gaussian 09, Revision B.01. Gaussian, Inc., Wallingford (2010)
45. Morakot, N., Rakrai, W., Keawwangchai, S., Kaewtong, C., Wanno, B.: Design and synthesis of thiourea based receptor containing naphthalene as oxalate selective sensor. J. Mol. Model. **16**, 129–136 (2010)
46. Jose, D.A., Singh, A., Das, A., Ganguly, B.: A density functional study towards the preferential binding of anions to urea and thiourea. Tetrahedron Lett. **48**, 3695–3698 (2007)
47. Bryantsev, V.S., Hay, B.P.: De novo structure-based design of bisurea hosts for tetrahedral oxoanion guests. J. Am. Chem. Soc. **128**, 2035–2042 (2006)
48. Steiner, T.: Hydrogen-bond distances to halide ions in organic and organometallic crystal structures: up-to-date database study. Acta Crystallogr. **B54**, 456–463 (1998)
49. Nandhakumar, R., Guo, Y.-E., Park, H., Tang, L., Nam, W., Kim, K.M.: A chiral ketone for enantioselective recognition of 1,2-amino alcohols. Tetrahedron Lett. **48**, 6582–6585 (2007)
50. Herrera, R.P., Monge, D., Martin-Zamora, E., Fernandez, R., Lassaletta, J.M.: Organocatalytic conjugate addition of formaldehyde *N*,*N*-dialkylhydrazones to β,γ-unsaturated α-keto esters. Org. Lett. **9**, 3303–3306 (2007)