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ORIGINAL ARTICLE

Anion binding properties of indolylmethanes

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Abstract The anion binding properties of the indolylmethanes (**1**) were investigated by ^{1}H-NMR spectroscopy in $CDCl_3$. Tris(3-methylindol-2-yl)methane (**1a**) selectively bound a chloride anion the over other tested anions (Br^-, I^-, HSO_4^-, and NO_3^-). In contrast, analogous compounds, phenyl bis(3-methylindol-2-yl)methane (**1b**), 2-hydroxyphenyl bis(3-methylindol-2-yl)methane (**1c**), tri(indol-3-yl)methane (**1d**), and phenyl di(indol-2-yl)methane (**1e**), showed a low anion binding ability and selectivity. These results indicate that the number and a position of the binding sites (indole NH protons) of the indolylmethanes are important factors for the formation of the complex with an anion. The high binding ability and selectivity of **1a** toward a chloride anion is attributed to the proper size of the binding pocket for a chloride anion and the formation of multiple hydrogen bonds between the three indole NH protons and a chloride anion. The anion affinity of **1a** was significantly affected by the cation component of quaternary ammonium salts, indicating that it is ion pair binding and not solely anion binding.

Keywords Anion recognition · Hydrogen bonding · Indolylmethane · Chloride anion selectivity · Quaternary ammonium salt

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Introduction

The development of anion receptors has received considerable attention because of their roles in chemical and biological processes [1]. Therefore, a considerable effort has been directed toward the design and synthesis of synthetic anion receptors. Artificial anion receptors have been constructed by introducing hydrogen bond donors, such as amide, urea, and thiourea groups, because anions are usually good hydrogen bond acceptors. However, in some cases, the weak anion binding ability of the amide, urea, and thiourea-based receptors is observed due to the competing intra- and intermolecular hydrogen bonds of their binding sites [2].

Indole is attractive as an anion-binding motif because the indole NH proton is a good hydrogen bond donor, which is less prone to be plagued by self-assembly [3]. Therefore, we conceived the idea to use indolylmethanes (Fig. 1) as an anion receptor of which the indole NH protons could be capable of simultaneously forming hydrogen bonds with an anion. We now describe the preparation and the anion complexation behavior of the indolylmethanes.

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 reference. 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

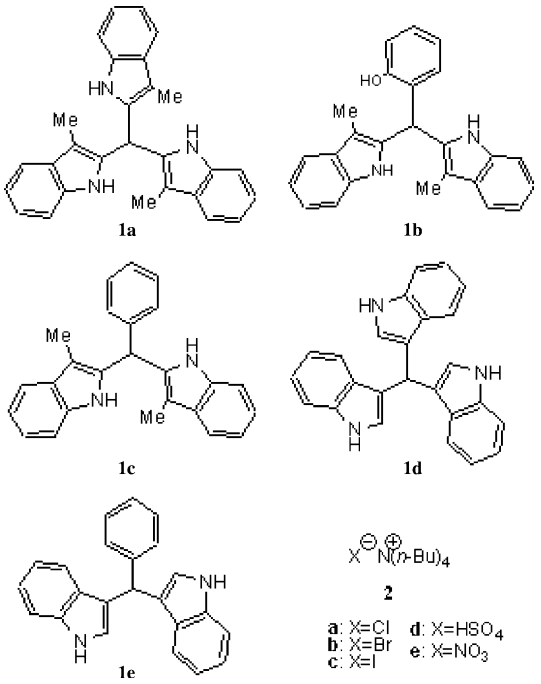


Fig. 1 Indolylmethanes (**1**) and quaternary ammonium salts (**2**)

reagent grade and were used without further purification. Indole, 3-methylindole, 3-formylindole, salicylaldehyde, benzaldehyde, triethyl orthoformate, tetra *n*-butyl ammonium slats, and montmorillonite K-10 clay were purchased from Kanto Chemical Co., Tokyo Kasei Industry and Aldrich.

Synthesis of tris(3-methylindol-2-yl)methane (1a)

A solution of the indole (792 mg, 6.0 mmol) in triethyl orthoformate (4.0 mL, 25 mmol) was adsorbed on montmorillonite K-10 clay (2.0 g) and heated at 70 °C for 6 h. The clay was leached with chloroform and the product was purified by column chromatography on silica gel using hexane:ethyl acetate=1:2 as an eluent to give brown powder, which was recrystallized from toluene to give **1a** (314 mg, 36% yield) as dark brown crystals.

1a: melting point 320–321 °C (lit. 319–320 °C) [4]. ^{1}H-NMR ($CDCl_3$) δ: 2.18 (s, 9H, Me), 6.22 (s, 1H, CH), 7.15 (ddd, 3H, Hc, $J = 1.5$, 7.0, 7.5 Hz), 7.18 (ddd. 3H, Hb, $J = 1.5$, 7.0, 7.5 Hz), 7.25 (dd, 3H, Ha, $J = 1.5$, 7.0 Hz), 7.58 (dd, 3H, Hd, $J = 1.5$, 7.5 Hz), 7.70 (bs, 3H, NH). ^{13}C-NMR($CDCl_3$) δ: 8.4, 33.6, 108.9, 111.1, 118.6, 119.7, 122.0, 129.5, 131.5, 135.3. IR (in $CHCl_3$, concentration = 10 mM): 3,442 (ν_{NH}) cm^{-1}. FAB-MS: 404 $(M + H)^+$. Elemental Analysis: Calcd. for $C_{28}H_{25}N_3$, C: 83.34%, H: 6.24%, N: 10.41%, Found: C: 83.54%, H: 6.04%, N: 10.22%.

Synthesis of 2-hydroxyphenyl bis(3-methylindol-2-yl) methane (1b)

To a solution of 3-methylindole (393 mg, 3.0 mmol) and salicylaldehyde (183 mg, 1.5 mmol) in methanol (5 mL) was added 37% hydrochloric acid aqueous solution (0.14 mL, 1.7 mmol) dropwise over 5 min at room temperature. After the addition was completed, the mixture was further stirred at room temperature for 4 h. The reaction mixture was diluted with chloroform (50 mL), and then was washed with water several times. The 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 using ethyl acetate : hexane, 1:2 as an eluent to give **1b** (218 mg, 40%) as yellowish crystals.

1b: melting point 230 °C (decomposed). ^{1}H-NMR ($CDCl_3$) δ: 2.17 (s, 6H, Me), 4.88 (bs, 1H, OH), 6.10 (s, 1H, CH), 6.87 (dd, 1H, Hh, $J = 1.5$, 7.5 Hz), 6.93 (ddd, 1H, Hf, $J = 1.5$, 7.5, 7.5 Hz), 7.05 (dd, 1H, He, $J = 1.5$, 7.5 Hz), 7.13 (ddd, 2H, Hc, $J = 1.5$, 7.5, 7.5 Hz), 7.16 (ddd, 2H, Hb, $J = 1.5$, 7.5, 7.5 Hz), 7.22 (ddd, 1H, Hg, $J = 1.5$, 7.5, 7.5) 7.25 (dd, 2H, Ha, $J = 1.5$, 7.5 Hz), 7.56 (dd, 2H, Hd, $J = 1.5$, 7.5 Hz), 7.79 (bs, 2H, NH). ^{13}C-NMR($CDCl_3$) δ: 8.5, 36.6, 108.9, 110.9, 116.9, 118.6, 119.5, 121.8, 121.9, 126.7, 129.0, 129.5, 129.9, 132.3, 135.3, 153.3. IR (in $CHCl_3$, concentration = 10 mM): 3,590 (ν_{OH}), 3,450 (ν_{NH}) cm^{-1}. FAB-MS: 367 $(M + H)^+$. Elemental Analysis: Calcd. for $C_{25}H_{22}N_2O$, C: 81.94%; H: 6.05%; N: 7.64%. Found: C: 82.22%; H: 5.98%; N: 7.56%.

Synthesis of phenyl bis(3-methylindol-2-yl)methane (1c)

To a solution of 3-methylindole (1.5 g, 11.5 mmol) and benzaldehyde (0.6 g, 5.7 mmol) in methanol (100 mL) was added 37% hydrochloric acid aqueous solution (0.47 mL, 5.6 mmol) dropwise over 5 min at room temperature. After the addition was completed, the mixture was further stirred at room temperature for 3.5 h. The reaction mixture was neutralized by addition of a sodium hydroxide aqueous solution (0.22 g of NaOH in 5.0 mL of water). Additional water (5.0 mL) was added, and after 1 h stirring at room temperature, the resulting suspension was filtered. The residue was dried in vacuo to give a yellowish powder as product (1.6 g, 78%).

1c: melting point 162–163 °C (lit. 156–158 °C) [5]. ^{1}H-NMR ($CDCl_3$) δ: 2.17 (s, 6H, Me), 5.99 (s, 1H, CH), 7.13 (ddd, 2H, Hc, $J = 1.5$, 7.0, 7.5 Hz), 7.15 (ddd, 2H, Hb, $J = 1.5$, 7.0, 7.5 Hz), 7.20 (dd, 2H, He, $J = 1.5$, 7.5 Hz), 7.24 (dd, 2H, Ha, $J = 1.5$, 7.0 Hz), 7.30 (m, 1H, Hg), 7.35 (m, 2H, Hf), 7.55 (m, 2H, Hd), 7.56 (bs, 2H, NH). ^{13}C-NMR($CDCl_3$) δ: 8.5, 40.9, 108.7, 110.8, 118.5, 119.5,

121.7, 127.3, 128.5, 129.0, 129.5, 133.4, 135.3, 140.0. IR (in $CHCl_3$, concentration = 10 mM): 3,460 (ν_{NH}) cm^{-1}. FAB-MS: 351 $(M + H)^+$. Elemental Analysis: Calcd. for $C_{25}H_{22}N_2$, C: 85.68%; H: 6.33%; N: 7.99%. Found: C: 85.88%; H: 6.42%; N: 7.75%.

Synthesis of tri(indol-3-yl)methane (1d)

A solution of indole (1.2 g, 10 mmol), 3-formylindole (0.53 g, 5 mol) in methanol (20 mL) was added a drop of 37% hydrochloric acid aqueous solution at room temperature. The mixture was refluxed for 1 h. After cooling to room temperature, the pale yellow precipitate was collected by filtration and then recrystallized from methanol to give **1d** (2.0 g, 55%) as brown crystals.

1d: melting point 253–254 °C (lit. 254–256 °C) [4]. ^{1}H-NMR ($CDCl_3$) δ: 6.18 (s, 1H, CH), 6.78 (m, 3H, Hi), 7.00 (ddd, Hc, J = 1.0, 7.5, 8.0 Hz, 3H), 7.16 (ddd, Hb, J = 1.0, 7.5, 8.0 Hz), 7.36 (dd, Ha, J = 1.0, 8.0 Hz), 7.51 (dd, Hd, J = 1.0, 8.0 Hz), 7.89 (bs, NH). ^{13}C-NMR ($CDCl_3$) δ: 31.2, 111.0, 119.0, 119.4, 120.1, 121.7, 123.3, 127.1, 136.7. IR (in $CHCl_3$, concentration = 10 mM): 3,480 (ν_{NH}) cm^{-1}. FAB-MS: 362 $(M + H)^+$. Elemental Analysis: Calcd. for $C_{25}H_{19}N_3$, C: 83.08%; H: 5.30%; N: 11.63%. Found: C: 82.89%; H: 5.60%; N: 11. 52%.

Synthesis of phenyl-di(indol-3-yl)methane (1e)

A mixture of indole (1.2 g, 10 mmol), benzaldehyde (0.53 g, 5.0 mol) and iodine (0.25 g, 1.0 mmol) in acetonitrile (50 mL) was stirred at room temperature for 20 min. Removal of acetonitrile by rotary evaporator gave dark brown oily residue, which was dissolved with ethyl acetate (50 mL). The solution was washed with 10% sodium thiosulfate aqueous solution (30 mL) two times. The organic layer was dried over anhydrous sodium sulfate. Removal of solvent gave solid residue, which was recrystallized from methanol to give **1e** (1.5 g, 92%) as yellowish crystals.

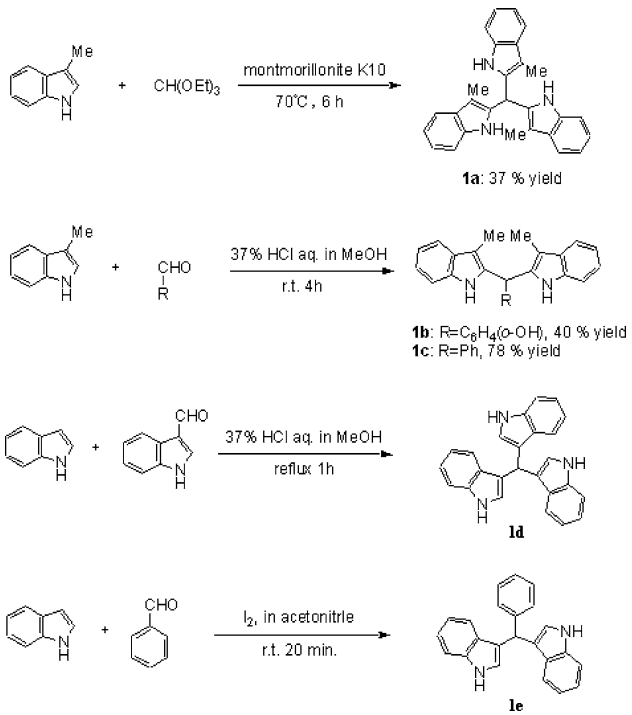
1e: melting point 123–124 °C (lit.125–126 °C) [4]. n^{1}H-NMR ($CDCl_3$) δ: 5.89 (s, 1H, CH), 6.66 (m, 2H, Hi), 7.00 (dd, 2H, Hc, J = 7.0, 8.0 Hz), 7.17 (dd, 2H, Hb, J = 7.0, 8.0 Hz), 7.21 (t, 1H, Hg, J = 7.0 Hz), 7.27 (dd, 2H, Hf, J = 7.0, 8.0 Hz), 7.34 (d, 2H, He, J = 8.0 Hz), 7.35 (d, 2H, Ha, J = 8.0 Hz), 7.39 (d, 2H, Hd, J = 8.0 Hz), 7.90 (bs, 2H, NH). ^{13}C-NMR ($CDCl_3$) δ: 40.1, 110.9, 119.2, 119.7, 119.9, 121.9, 123.5, 126.1, 127.0, 128.1, 128.6, 136.6, 143.9. IR (in $CHCl_3$, concentration = 10 mM): 3,485 (ν_{NH}) cm^{-1}. FAB-MS: 323 $(M + H)^+$. Elemental Analysis: Calcd. for $C_{23}H_{18}N_2$, C: 85.68%; H: 5.63%; N: 8.69%. Found: C: 85.78%; H: 5.40%; N: 8.55%.

Job plot

The ^{1}H-NMR sample solutions were made of [**1**]/[**2**] ratios under the condition that [**1**] + [**2**] = 3.0 mM in $CDCl_3$, and [**2**] varies from 0 mM 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 NH proton of **1** that is sensitive to complex formation. The data were plotted in the form $\Delta\delta \times$ [**1**] vs. [**1**]/([**1**] + [**2**]), and the position of the maximum indicates the stoichiometry of the complex.

^{1}H-NMR titration

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 (**2**) stock solution (concentration = 10.0 mM) in $CDCl_3$ to a solution of indolylmethanes (**1**) (700 μL, concentration = 5.76 mM) in $CDCl_3$. A 1:1 association of indolylmethanes (**1**) and quaternary ammonium salts (**2**) 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.



Scheme 1 Synthesis of indolylmethanes (**1**)

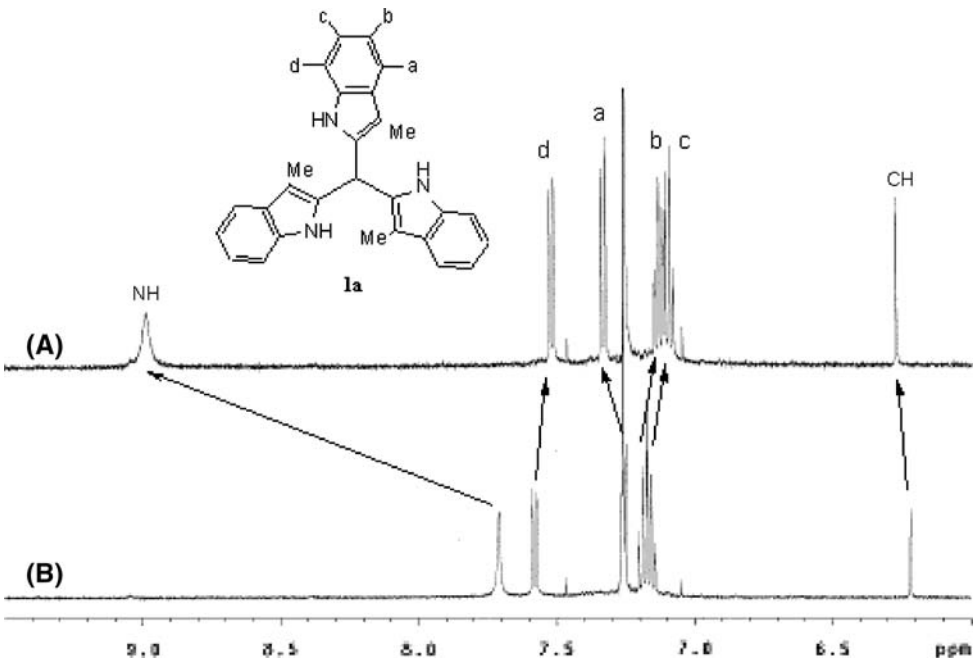


Fig. 2 ^{1}H-NMR spectra of tris(3-methylindol-2-yl)methane (**1a**) in $CDCl_3$ at 297 K. (**a**) **1a** + **2a**; (**b**) **1a**. ([**1a**] = [**2a**] = 3.0 mM)

Results and discussion

The indolylmethane derivatives (**1a–e**) were synthesized as shown in Scheme 1. Tris(3-methylindol-2-yl)methane (**1a**) was prepared by the solvent-free reaction of 3-methylindole with triethyl orthoformate on activated montmorillonite K 10 clay at 70 °C for 10 h in 37% yield according to the literature [4]. 2-Hydroxyphenyl bis(3-methylindol-2-yl)methane (**1b**) and phenyl bis(3-methylindol-2-yl)methane (**1c**) were synthesized by the reaction of 3-methylindole and salicylaldehyde or benzaldehyde in the presence of HCl in ethanol at room temperature for 7 h in 40% (**1b**) and 78% (**1c**) yields, respectively [5]. A similar reaction of 3-formylindole with two equimolar amount of indole produced the tri(indol-3-yl)methane (**1d**) in 55% yield [4]. Phenyl di(indol-3-yl)methane (**1e**) was synthesized from the reaction of the indole and benzaldehyde in the presence of iodine in acetonitrile at room temperature in 92% yield [6]. The structures of these indolylmethane derivatives (**1a–e**) were based on their spectral and analytical data (^{1}H-NMR, ^{13}C-NMR, IR, MS, and elemental analysis).

The ability of these indolylmethane derivatives (**1**) to act as anion receptors was investigated by ^{1}H-NMR experiments in $CDCl_3$. The addition of one equimolar amount of the tetra *n*-butyl ammonium chloride (**2a**) to a solution of tris(3-methylindol-2-yl)methane (**1a**) in $CDCl_3$

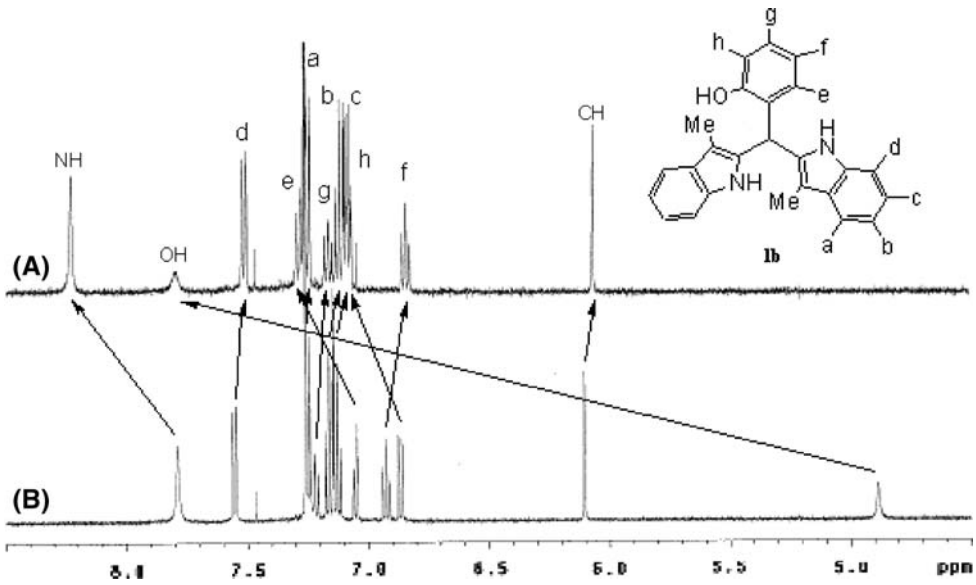


Fig. 3 ^{1}H-NMR spectra of 2-hydroxyphenyl bis(3-methylindol-2-yl)methane (**1b**) in $CDCl_3$ at 297 K. (**a**) **1b** + **2a**; (**b**) **1b**. ([**1b**] = [**2a**] = 3.0 mM)

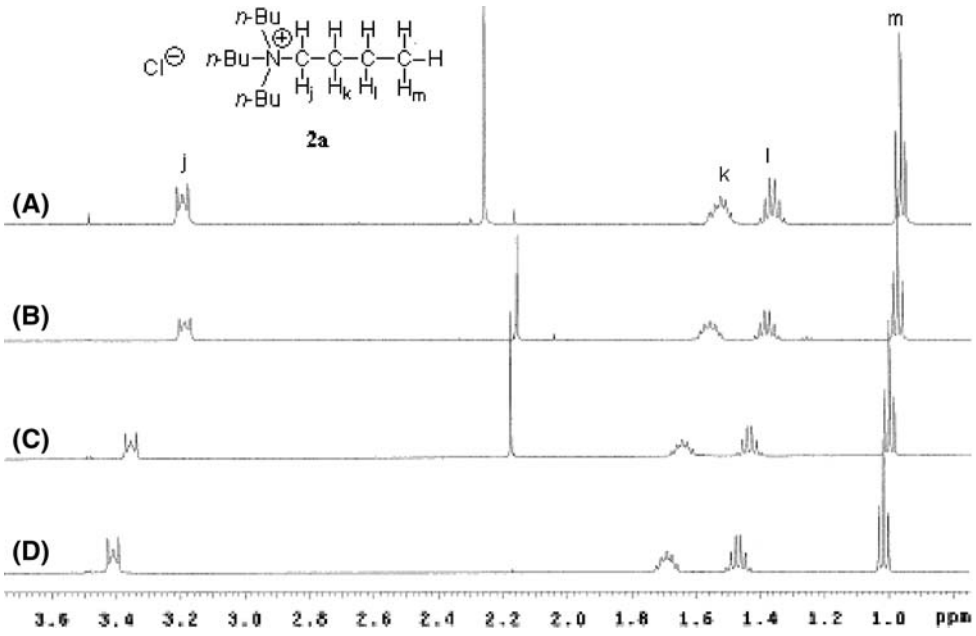


Fig. 4 ^{1}H-NMR spectra of tetra *n*-butyl ammonium chloride (**2a**) in $CDCl_3$ at 297 K. (**a**) **1a** + **2a**; (**b**) **1b** + **2a**; (**c**) **1c** + **2a**; (**d**) **2a**. ([**1a**] = [**1b**] = [**1c**] = [**2a**] = 3.0 mM)

([**1a**] = [**2a**] = 3 mM) produced a remarkable downfield shift of the NH proton resonance of **1a** in the ^{1}H-NMR spectrum (Fig. 2). The NH proton chemical shift changed from δ 7.70 ppm to δ 8.77 ppm ($\Delta\delta_{NH}$ = +1.07 ppm) in the presence of **2a**. The large downfield shift indicates the formation of hydrogen bonds between the three NH protons of **1a** and chloride anion of **2a**. Similar ^{1}H-NMR induced chemical shift changes in the NH protons of indolylmethanes (**1b** ($\Delta\delta_{NH}$ = +0.44 ppm), **1c** ($\Delta\delta_{NH}$ = +0.26 ppm), **1d** ($\Delta\delta_{NH}$ = +0.14 ppm), **1e** ($\Delta\delta_{NH}$ = +0.24 ppm)) were observed due to the interaction between the other indolylmethanes (**1b–1e**) and tetra *n*-butyl ammonium chloride (**2a**) (Fig. 3). Interestingly, the phenolic OH proton of **1b** also fairly shifted downfield ($\Delta\delta_{OH}$ = +2.91 ppm), indicating the participation of the OH proton in the formation of the complex (**1b–2a**) [7, 8].

On the other hand, the resonances of the *n*-butyl groups of **2a** shifted upfield in the presence of the indolylmethanes (**1**). The induced chemical shift changes ($\Delta\delta$) of the *n*-butyl groups of **2a** increased due to the protons near the cation moiety (N^+) of the quaternary ammonium component (Fig. 4). This order ($\Delta\delta_{Hj} > \Delta\delta_{Hk} > \Delta\delta_{Hl} > \Delta\delta_{Hm}$) is compatible to the acidity of the protons. Therefore, it is likely that the upfield shift of the *n*-butyl groups is the main

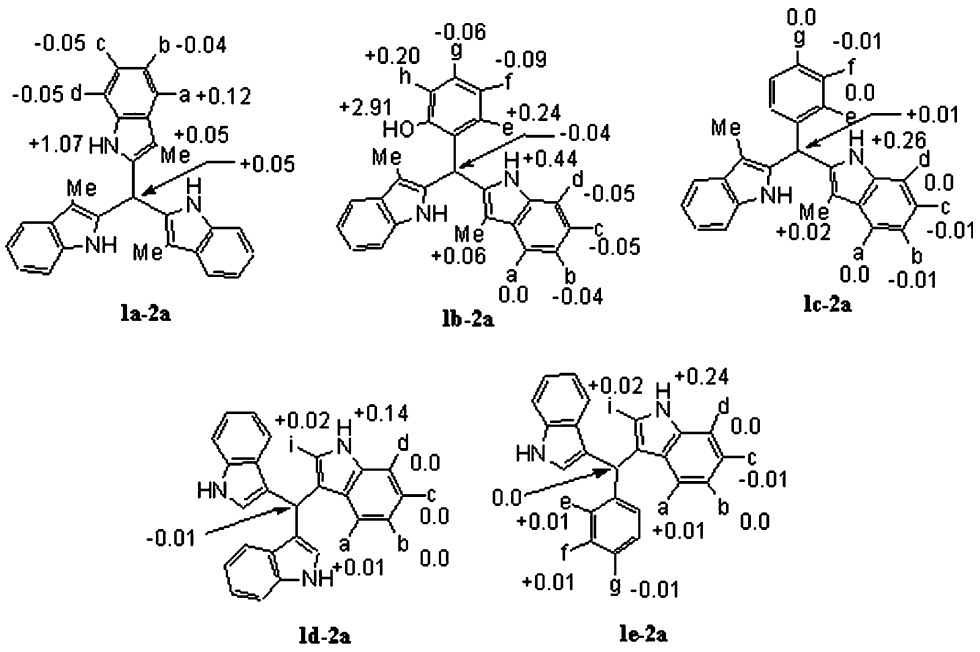


Fig. 5 Induced chemical shift [ppm] of **1** in the presence of **2a** at 24 °C in $CDCl_3$ ([**1**] = [**2a**] = 3.0 mM). − denotes the shift to higher magnetic field

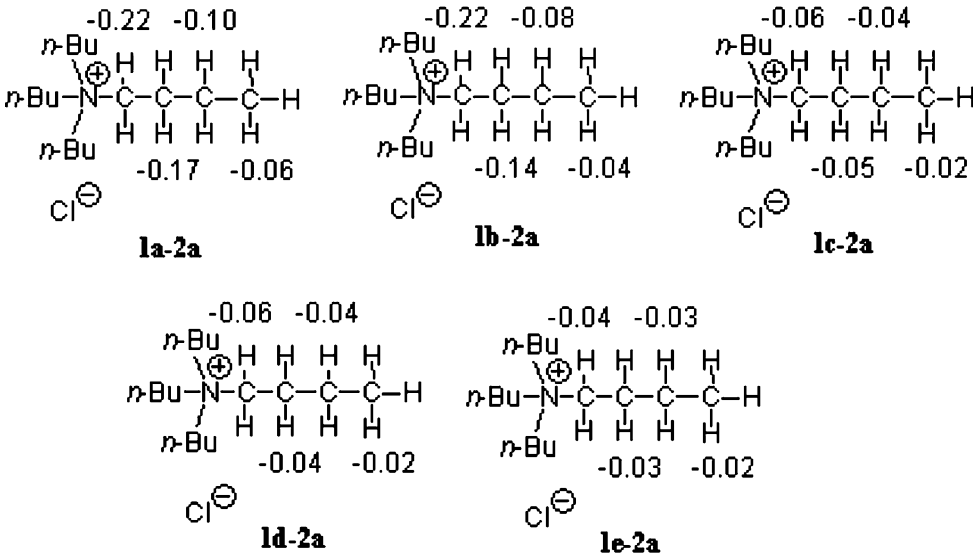


Fig. 6 Induced chemical shift [ppm] of **1** in the presence of **a** at 24 °C in $CDCl_3$ ([**1**] = [**2a**] = 3.0 mM). − denotes the shift to higher magnetic field

cause of a cation-π interaction between the quaternary ammonium part of **2** and the aromatic moieties of the indolylmethanes (**1**) [9]. The values of the induced ^{1}H-NMR chemical shift changes ($\Delta\delta$) in **1** and **2a** are summarized in Figs. 5 and 6.

In order to obtain further information concerning the interaction between **1** and **2**, variable temperature ^{1}H-NMR measurements were carried out. The temperature dependencies of the exchangeable protons, such as the amide NH protons, are used to elucidate the hydrogen bonding in peptide chemistry [10]. In a non-polar solvent such as $CDCl_3$, amide protons that are either not hydrogen bonded or locked in a hydrogen-bonded state exhibit small temperature dependencies in the chemical shifts, while the amide protons that participate in an equilibrium between a hydrogen-bonded state and a non-hydrogen-bonded state exhibit large temperature dependencies. By applying it to our system, the indole NH protons changed in the presence of a chloride anion (**2a**) ($\Delta\delta/\Delta T$ [ppb/K] = −7.5 (**1a**), −3.5 (**1b**), −3.2 (**1c**), −3.2 (**1d**), −3.3 (**1e**)). On the other hand, there was no appreciable change in the indole NH protons in the absence of a chloride anion (**2a**) ($\Delta\delta/\Delta T$ [ppb/K] = −0.7 (**1a**), −0.7 (**1b**), −0.7 (**1c**), −1.7 (**1d**), −1.7 (**1e**)) as shown in Figs. 7 and 8. The OH proton of **1b**

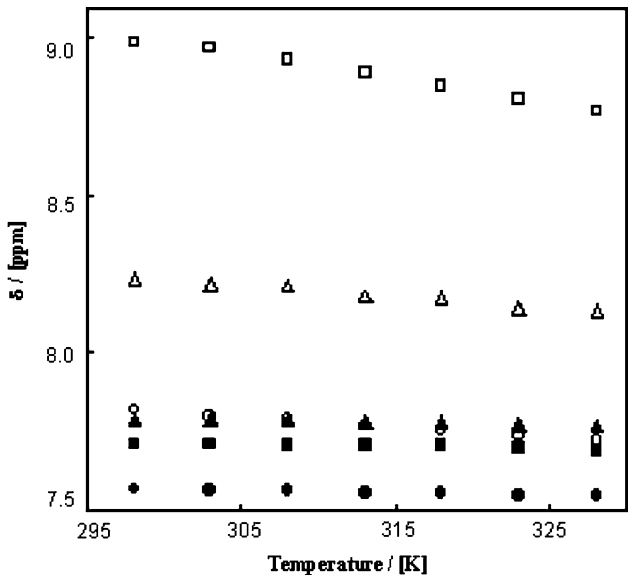


Fig. 7 ^{1}H-NMR chemical shifts (δ values) of NH protons of indol-2-ylmethanes (**1a**, **1b**, **1c**) (3.0 mM) in the presence (**1a**:□, **1b**:Δ, **1c**:◯) and absence (**1a**:■, **1b**:Δ, **1c**:●) of **2a** (3.0 mM) as a function of temperature [K] in $CDCl_3$

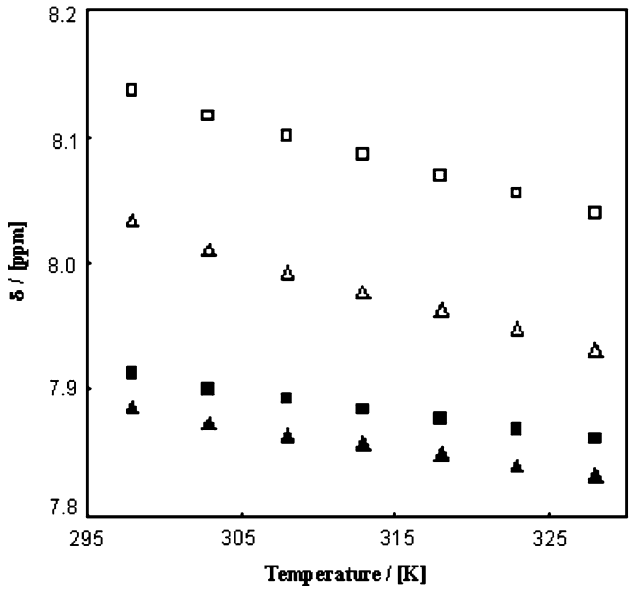


Fig. 8 ^{1}H-NMR Chemical shifts (δ values) of NH protons of indol-3-ylmethanes (**1d**, **1e**) (3.0 mM) in the presence (**1d**:□, **1e**:Δ) and absence (**1d**:■, **1e**:Δ) of **2a** (3.0 mM) as a function of temperature [K] in $CDCl_3$

was more sensitive to the temperature and showed a considerable change in the presence of a chloride anion (**2a**) ($\Delta\delta/\Delta T$ [ppb/K] = −25.7 (**1b**)), while the temperature dependence ($\Delta\delta/\Delta T$) is −1.4 [ppb/K] in the absence of a chloride anion as shown in Fig. 9. These temperature dependencies suggest that the NH and OH protons of **1** in the presence of a chloride anion (**2a**) equilibrate between the hydrogen-bonded and non-hydrogen-bonded states and provide further support that the NH and OH protons of **1** are the anion binding sites.

We estimated the stoichiometry of the complexes (**1–2**) using the Job plot method [11]. The 1:1 stoichiometry of the complexes (**1–2**) was confirmed by a plot that contains a maximum at the mole ratio of 0.5 in these cases, with the exception of the complex between **1d** and **2**, of which the plot contains a maximum at the mole ratio of 0.6, indicating a complicated complexation (Figs. 10, 11). Association studies were conducted by titrating the $CDCl_3$ solutions of the receptors (**1**) with incremental amounts of the anions (**2**) as shown in Fig. 12 and monitoring the downfield shift of the indole NH proton resonances of **1**. Analysis of the data according to the non-linear regression method [12] provided the association constants (K_a) reported in Table 1. The anion binding ability of the indolylmethanes (**1**) was in the following order: (**1a**: $Cl^- \gg Br^- > NO_3^- \approx HSO_4^- \approx I^-$; **1b**, **1c**, and **1e**: $Cl^- > NO_3^- > Br^- \approx I^- \approx HSO_4^-$ [13]). Tris(3-methylindol-2-yl)methane (**1a**) showed a chloride anion selectivity which was not in accord with the basicity of anions [14]. Chloride anion is one of the anions expected to produce a stronger hydrogen bonding due to its comparatively smaller size. Therefore, the chloride anion could efficiently form hydrogen bonds with the binding pocket of tris(3-methylindol-2-yl)methane (**1a**), which is constructed from three indole NH protons. The number of binding sites (NH protons) will be an important factor in the recognition of the anions, because the association constants of the phenyl-bis(3-methylindol-3-yl)methane (**1c**), which has two indole NH protons, were smaller than that of **1a** (K_a (**1a–2a**) = 1,200 M^{-1}; K_a (**1c–2a**) = 75 M^{-1}). Although 2-hydroxyphenyl-bis(3-methyl-indol-2-yl)methane (**1b**) has two NH protons and a phenolic OH proton, which is a

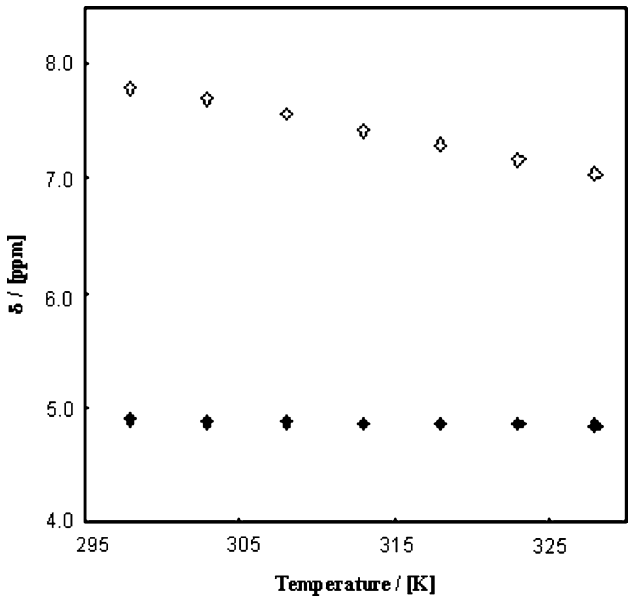


Fig. 9 ^{1}H-NMR chemical shifts (δ values) of OH protons of **1b** (3.0 mM) in the presence (◇) and absence (◆) of **2a** (3.0 mM) as a function of temperature [K] in $CDCl_3$

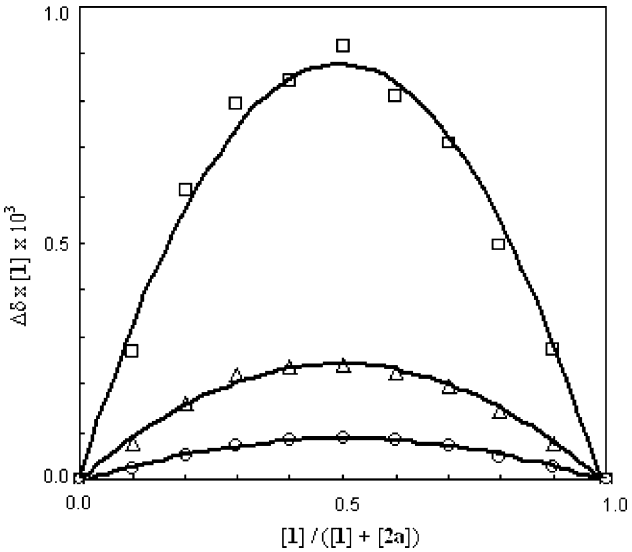


Fig. 10 Job plots of indol-2-ylmethanes (**1a–1c**) with quaternary ammonium chloride (**2a**) (**1a** and **2a** (□), **1b** and **2a** (Δ), **1c** and **2a** (◯))

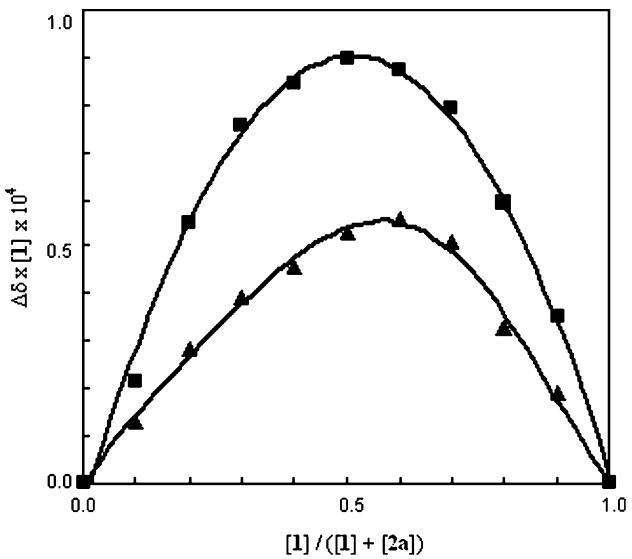


Fig. 11 Job plots of indol-3-ylmethanes (**1d, 1e**) with quaternary ammonium chloride (**2a**) (**1d** and **2a**:(■), **1e** and **2a:**(▲))

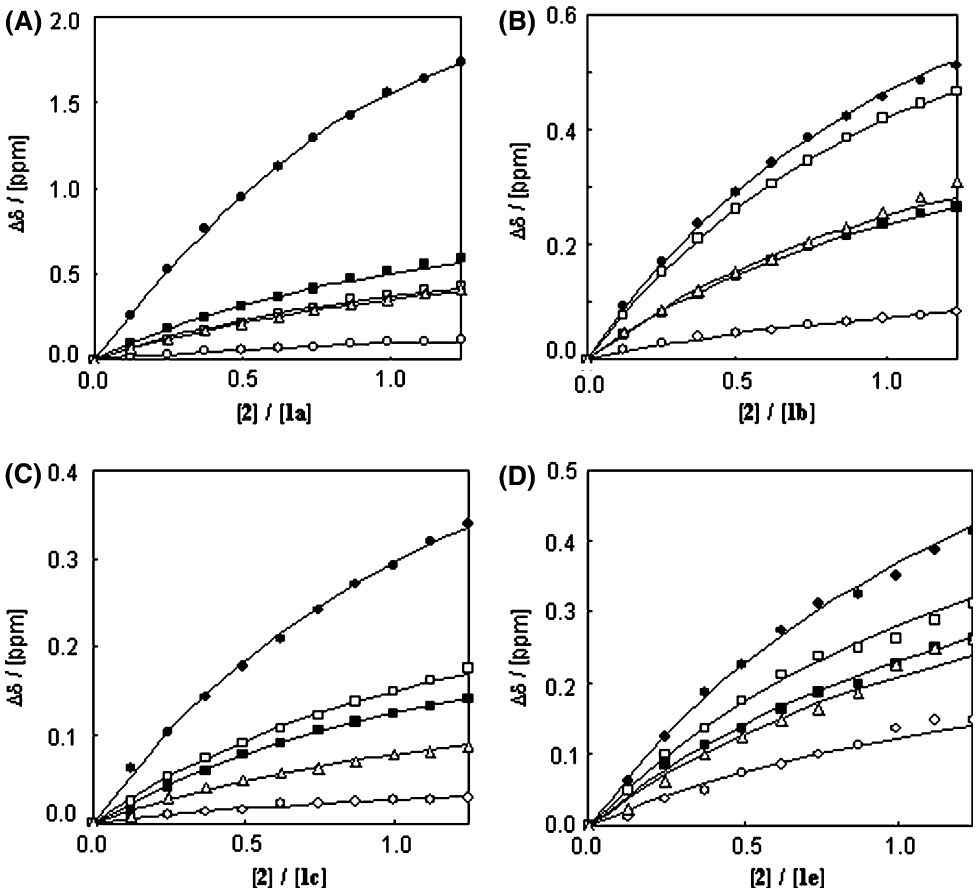


Fig. 12 ^{1}H-NMR titration of **1a** with **2** (**a**), **1b** with **2** (**b**), **1c** with **2** (**c**), **1e** with **2** (**d**) in $CDCl_3$ at 297 K. Indicated a change in the chemical shift of the NH protons of **1** as a result of added **2**. Plots are experimental data and curves are calculated by non-linear regression. (Cl^- (**2a**): ●, Br^- (**2b**): ■, I^- (**2c**): ◯, HSO_4^- (**2d**): △, NO_3^- (**2e**): □)

more acidic proton compared to the indole NH proton, **1b** is less bound to a chloride anion compared to **1a** (K_a (**1b–2a**) = 150 M^{-1}), suggesting that a chloride anion fits better into the cavity of **1a** than that of **1c**. The smaller induced chemical shift values and the lower association constants of the indol-3-ylmethanes (**1d** and **1e**) compared to those of the indol-2-ylmethanes (**1a** and **1c**) indicate that the position of the binding sites (NH protons) will also be an indispensable factor for the anion recognition.

Table 1 Association Constants (K_a [M^{-1}] in $CDCl_3$ at 297 K) for 1:1 complexes of indolylmethanes (**1**) and quaternary ammonium salts (**2**) and free energy ($-\Delta G$ [kJ/mol] in $CDCl_3$ at 297 K)

Association constants (K_a) [M^{-1}][a] (free energy ($-\Delta G$ [kJ/mol]))				
Anion[b]	Host			
	1a	**1b**	**1c**	**1e**
Cl^- (**2a**)	1,200 (17.5)	150 (12.4)	75 (10.7)	26 (8.0)
Br^- (**2b**)	105 (11.5)	55 (9.9)	25 (7.9)	16 (6.8)
I^- (**2c**)	27 (8.1)	16 (6.8)	22 (7.6)	7 (4.8)
HSO_4^- (**2d**)	34 (8.7)	27 (8.1)	12 (6.1)	13 (3.2)
NO_3^- (**2e**)	36 (8.8)	125 (11.9)	31 (8.5)	23 (7.7)

[a] Errors were estimated to be 10%

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

We also investigated the counter cation effect on the anion recognition of the tris(3-methylindol-2-yl)methane (**1a**) using trimethyl benzyl ammonium chloride (**3a**) and triethyl benzyl ammonium chloride (**3b**). The association constant between **1a** and **3b** (K_a(**1a–3b**) = 900 M^{-1}) is greater than that of **1a–3a** (K_a(**1a–3a**) = 380 M^{-1}). Considering that quaternary ammonium salts form a tight ion-pair in non-polar solvents, such as chloroform, it is interactive for an anion receptor to be significantly separated between the cation and the anion components in the quaternary ammonium salt. Therefore, a chloride anion of the triethyl benzyl ammonium salt (**3b**) can be strongly interactive with the indole NH protons of **1a** compared to that of the trimethyl benzyl ammonium salt (**3a**).

In summary, we investigated the anion recognition properties of the indolylmethanes and found that the number and position of the binding sites (indole NH protons) of the indolylmethanes are important factors for the anion recognition. A chloride anion selectivity was observed using tris(3-methylindol-2-yl)methane (**1a**) as an anion receptor. This selectivity is attributed to the size and shape of a chloride anion towards a binding pocket, which was constructed from the three indole moieties of **1a**. The association constants for 1:1 complexes of **1a** with quaternary ammonium salts was found to be significantly

affected by the cation component of quaternary ammonium salts (**2a**, **3a**, and **3b**), indicating that it is ion pair binding which they are observing and not solely anion binding.

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