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An ion pair receptor showing remarkable enhancement of anion-binding strengths in the presence of alkali metal cations

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Abstract—An ion pair receptor was prepared by coupling of a diazacrown ether and a rigid biindole scaffold bearing hydrogen bond donors of two indole NHs. The former serves as the cation-binding site and the latter functions as the anion-binding site. The anion-binding affinities to the receptor, determined by ^1H NMR titration experiments in 10% (v/v) DMSO-d_6/CD$_3$CN at 24 ± 1 °C, have been greatly improved when an alkali metal cation binds to the adjacent diazacrown ether. For example, the association constant between chloride and receptor alone is 7 M^{-1}, but the magnitudes increase into 120 M^{-1}, 14,000 M^{-1}, and 6200 M^{-1} in the presence of lithium, sodium, and potassium ions, respectively. The enhanced binding affinities must be attributed to electrostatic interactions by possibly forming contact ion pairs.

A large variety of synthetic receptors binding either a cation or an anion have been intensively prepared over the last four decades.[1] The binding properties of these receptors with target ions have been frequently characterized using organic salts, for example, picrate for cations and tetrabutylammonium for anions, which minimize adverse counterion effects on the binding strengths. To circumvent this shortcomings, ditopic receptors capable of simultaneously binding both a cation and an anion as an ion pair have been studied in recent years.[2] The ion pair receptors have been proven more effective on the solubilization and extraction of salts in organic solvents, and the transport through liquid membranes relative to the receptors binding either a cation or an anion alone.

The ion pair receptors must possess both cation- and anion-binding sites, which are delicately placed in right distance and geometry able to form contact ion pair. Otherwise high unfavorable energy is required for the charge separation, which leads to decreasing the binding affinity. A number of ion pair receptors have been reported to date.[3–5] Crown ethers[4] and calixarenes[5] have been frequently utilized as cation-binding units, and hydrogen-bonding donors such as amido and ureido functionalities have been commonly incorporated for

binding anions.[3–5] Herein, we have prepared an ion pair receptor **3**, which exhibits dramatic increases in halide-binding abilities when alkali metal cations are
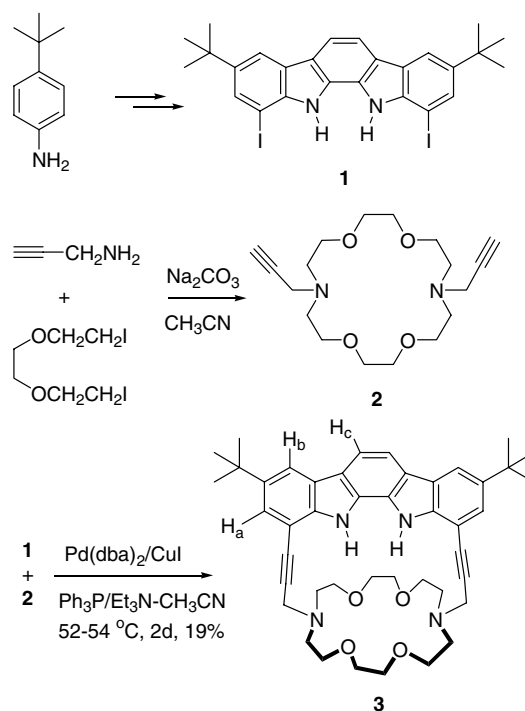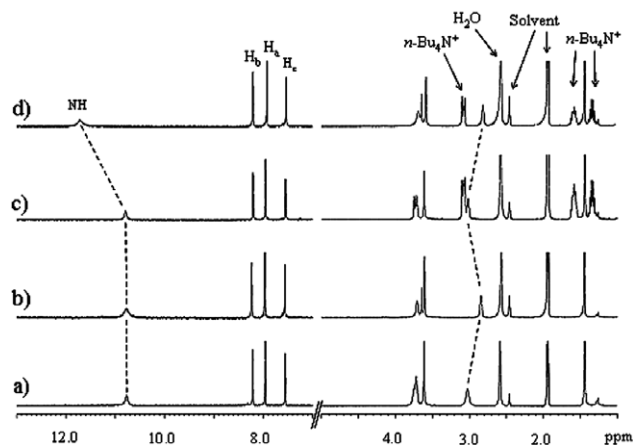

Scheme 1. Synthesis of receptor **3**.

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coordinated to the adjacent crown ether unit (see Scheme 1). The cation effects on the binding strengths become pronounced in the order of $Li^+ < K^+ < Na^+$, regardless of the kind of halides.

Utilizing an indole scaffold as a molecular building block, we[6] and others[7] have recently prepared a number of anion receptors able to bind anions based on hydrogen-bonding interactions. Here, a rigid biindole scaffold **1** with two indole NHs has been employed as hydrogen bond donors. Diaza-18-crown-6 **2**, prepared according to a literature procedure,[8] has been selected as the cation-binding site. Compound **1** was synthesized from 4-*tert*-butylaniline as described previously in our laboratory.[6a,c] The Pd(0)/CuI-catalyzed coupling[9] of **1** with **2** afforded receptor **3** in 19% yield.[10]

First, the binding properties of **3** were qualitatively investigated by ^1H NMR spectroscopy in a polar medium, 10% (v/v) DMSO-d_6/CD$_3$CN. When potassium hexafluorophosphate (1 equiv) was added to receptor **3** (1 mM), the CH signals of the diaza crown unit were shifted by $\Delta\delta = 0.1$–0.2 ppm as a result of potassium binding, while no chemical shift change was observed for indole NHs (Fig. 1b). In addition, the ^1H NMR spectrum of **3** was almost unchanged ($\Delta\delta = 0.02$ ppm for the indole NH signal) upon addition of tetrabutylammonium chloride (Fig. 1c). However, the NH signal was considerably downfield shifted ($\Delta\delta = \sim1$ ppm) when both potassium hexafluorophosphate (1 equiv) and tetrabutylammonium chloride (1 equiv) were added (Fig. 1d). These spectral observations suggest that chloride binds more strongly to receptor **3** in the presence of potassium ion.

Quantitative analyses for the binding behaviors were performed by the ^1H NMR titrations in 10% (v/v) DMSO-d_6/CD$_3$CN at 24 ± 1 °C. Lithium perchlorate (LiClO$_4$), sodium perchlorate (NaClO$_4$), and potassium hexafluorophosphate (KPF$_6$) were selected as sources of alkali metal cations because of their sufficient solubility

and the negligible binding ability of the counteranions (ClO$_4^-$, PF$_6^-$) in these conditions. Halides were used as tetrabutylammonium salts (*n*-Bu$_4$N$^+$X$^-$). First, the binding affinity between chloride and **3** was revealed in the absence of any alkali metal salt. Upon addition of chloride (up to 100 equiv), the NH signal of **3** was slowly shifted downfield by approximately 0.5 ppm as a result of forming hydrogen bonds, which yielded the association constant (K_a) of 7 ± 2 M^{-1}. Larger halides, Br$^-$ and I$^-$, showed similar trends but the magnitudes of complexation-induced shifts (CIS) were too small ($\Delta\delta < 0.2$ ppm) to accurately determine the association constants.

Next, the titrations were carried out in the presence of alkali metal salts to reveal the cation effect on the binding affinity of halides to **3**. Addition of a halide to a solution containing 1:1 ratio of **3** and alkali metal salts (1.0×10^{-3} M) results in large downfield shifts of the NH signals. In addition, three aromatic CH signals are slightly upfield shifted by 0.01–0.06 ppm during the titration. As shown Figure 2 (top), the titration curves are much steeper and the magnitudes of the CIS values are much larger compared with the one observed without an alkali metal salt. The association constants were
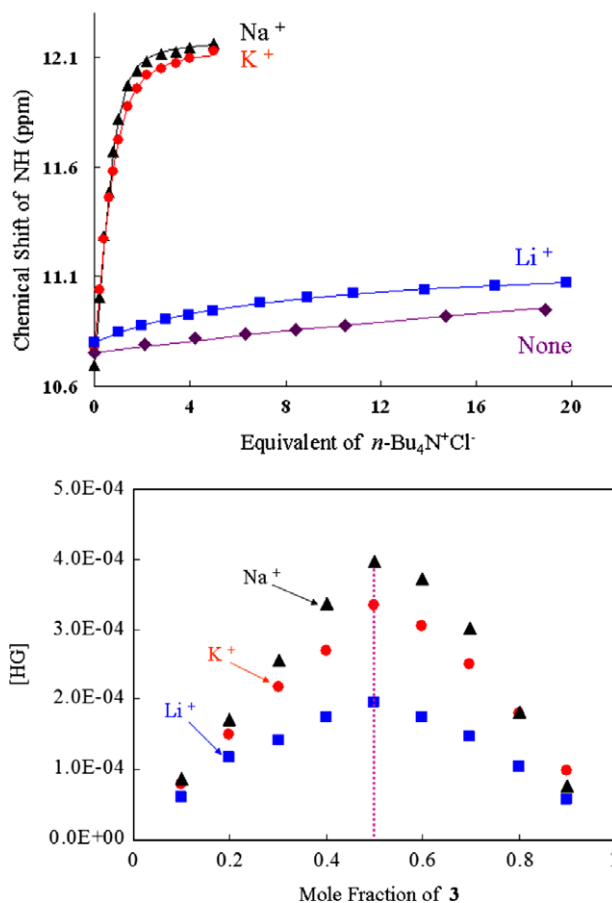
Figure 2. Titration curves (top) and Job's plots (bottom) (10% v/v DMSO-d_6/CD$_3$CN, 24 ± 1 °C) between **3** and tetrabutylammonium chloride in the presence of alkali metal salts (1 equiv): none (purple diamond) LiClO$_4$ (blue square), NaClO$_4$ (black triangle), and KPF$_6$ (red circle).

Figure 1. Partial ^1H NMR spectra (400 MHz, 10% v/v DMSO-d_6/CD$_3$CN, 25 °C) of **3** (1.0 mM) in the presence of (a) none, (b) KPF$_6$ (1 equiv), (c) *n*-Bu$_4$N$^+$Cl$^-$ (1 equiv), and (d) KPF$_6$ (1 equiv)+*n*-Bu$_4$N$^+$Cl$^-$ (1 equiv).

Table 1. Association constants (K_a, M^{-1}) between ion pair receptor **3** and halides in the presence of alkali metal salts (1 equiv) in 10% (v/v) DMSO-d_6/CD$_3$CN at 24 ± 1 °C[a]

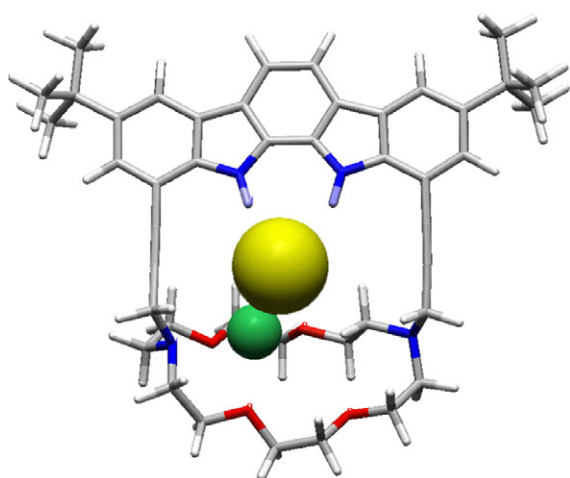| Halide[b]	Cation additive	Association constant
Cl$^-$	None	7
	Li$^+$ClO$_4$	120
	Na$^+$ClO$_4$	14,000
	K$^+$PF$_6$	6200
Br$^-$	None	—[c]
	Li$^+$ClO$_4$	24
	Na$^+$ClO$_4$	600
	K$^+$PF$_6$	200
I$^-$	None	—[c]
	Li$^+$ClO$_4$	9
	Na$^+$ClO$_4$	61
	K$^+$PF$_6$	45

[a] Titration experiments were all duplicated in the ^{1}H NMR spectroscopy, and the association constants were analyzed based on the downfield shifts of the indole NH signals. Errors in the association constants are less than 15% except those of $K_a < 10$ M^{-1} in which cases errors increase up to 30%.

[b] Halides were used as tetrabutylammonium salts.

[c] The chemical shift changes during the titration were too small to determine the association constant.

determined by nonlinear least squares fitting analysis[11] with the expression of a 1:1 binding isotherm and the results are summarized in Table 1. The 1:1 complex formation was also confirmed by the continuous variation method (Fig. 2, bottom Job's plot).[12]

Two trends are apparent. First, the association constants of halides to **3** greatly increase in the presence of alkali metal cations.[13] For example, the association constants of chloride are 120 M^{-1}, 14,000 M^{-1}, and 6200 M^{-1}, in the presence of lithium, sodium, and potassium ions, respectively. These are up to 2000-fold higher than that (7 M^{-1}) without any alkali metal cation, which corresponds to the free energy difference of $\Delta\Delta G = -4.4$ kcal/mol. Second, in all cases studied here sodium ion shows the highest cooperative effect on the

anion-binding strengths, followed by potassium ion then lithium ion. The enhanced binding affinities of halides must be attributed to electrostatic interactions with alkali metal cations. This interaction depends on the charge density as well as the inter-ionic distance, which in our system is seemingly optimal with sodium ion. According to computer modeling (Fig. 3),[14] chloride ion is stabilized not only by two hydrogen bonds with indole NHs but also by forming contact ion pair with sodium ion binding to the adjacent crown ether moiety by ion–dipole interactions.

In conclusion, an ion pair receptor has been prepared, which consists of two different binding subunits, an aza-crown ether unit for binding alkali metal cations and a biindole scaffold for hydrogen-bonding with halides. The receptor exhibits high cooperative binding of a cation and an anion; in the presence of alkali metal salts the binding affinities of halides greatly increase up to three orders of magnitudes. The modification of this receptor is currently undergoing to develop a molecular sensor able to show a color change upon binding a specific salt.

Figure 3. An energy-minimized structure of complex **3**·NaCl generated with MMFF force field (MacroModel 7.1).[14]

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10. *Synthesis and physical properties of* **3**: Diiodobiindole **1** (1.0 g, 1.6 mmol), CuI (15 mg, 0.05 equiv) and Pd(dba)₂ (467 mg, 0.05 equiv), PPh₃ (0.11 g, 0.25 equiv) were placed in a Schlenk flask. The flask was degassed under high vacuum and back-filled with nitrogen, which process was repeated three times and degassed CH_3CN (10 mL) and Et_3N (30 mL) were added (solution A). Likewise, a solution of diazacrown ether **2** (0.55 g, 1.0 equiv) in

degassed CH_3CN (10 mL) and Et_3N (30 mL) was sepa-rately prepared and was added via a cannula to the solution A. The solution was stirred under nitrogen at 52–54 °C for 1 day, and then cooled down to ambient temperature. The mixture was filtered through Celite and the filtrate was concentrated. The residue was dissolved in CH_2Cl_2 (70 mL), and washed with distilled water. After concentration, the residue was purified by sequential column chromatography (silica gel, the first column chromatography with CH_2Cl_2/MeOH = 20:1, and the second column chromatography with THF/CH_2Cl_2 = 1:1) and the product was washed several times with deionized water to give **3** (0.21 g, 19%) as off-white soilds. The yield was approximately 40% based on ^{1}H NMR integration, but the isolated yield is low due to the repeated purifica-tion by column chromatography followed by washing with deionized water: mp 166–167 °C; ^{1}H NMR (400 MHz, CDCl₃) δ 10.45 (s, 2H; NH), 8.12 (s, 2H), 7.93 (s, 2H), 7.53 (s, 2H), 3.79–3.82 (m, 8H), 3.74–3.76 (m, 8H), 3.69 (s, 4H), 3.06 (t, 8H, $J = 6.2$ Hz), 1.45 (s, 18H); ^{13}C NMR (100 MHz, CDCl₃) δ 142.2, 139.0, 130.0, 126.5, 119.9, 119.6, 118.2, 116.9, 105.1, 89.5, 81.0, 70.2, 68.1, 55.0, 41.3, 40.4, 31.7; IR (KBr) 3485, 2226, 1630, 1454 cm^{-1}; HRMS (ES-TOF) *m/z* for $C_{44}H_{54}N_4O_4$ calcd 725.4037, found 725.4039.

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13. Due to the limited solubility of alkali metals salts in organic solvents, the association constants could not be determined in the presence of large excess of alkali metals salts. Under the conditions we studied here, the crown ether is partially occupied by an alkali metal cation. Therefore, the association constants in Table 1 must be smaller than those anticipated from the complete coordi-nation of an alkali metal cation to the adjacent crown ether.

14. The modeling study was carried out using MMFF force field implemented in MacroModel 7.1 program on a Silicon Graphics Indigo IMPACT workstation. To find an energy-minimized structure, 1000 separate search steps were conducted with a Monte Carlo conformational search. In the energy-minimized structure, the distance between Na$^+$ and Cl$^-$ is 2.60 Å and two hydrogen bond distances of N (indole) and Cl$^-$ are 3.36 Å and 3.63 Å. These distances are comparable to those (2.70 Å for Na$^+$···Cl$^-$ and 3.35 Å for N···Cl$^-$) reported by Smith and co-workers in Ref. 5b based on the crystal structure of the complex showing a binding mode of the contact ion pair between a ditopic receptor, Na$^+$ and Cl$^-$.