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Biindolyl-based molecular clefts that bind anions by hydrogen-bonding interactions

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Abstract—Molecular clefts were synthesized from 2,2′-biindolyl scaffold that contains good hydrogen bond donors of two indole NHs. The molecular clefts were systematically modified in two different manners to increase binding affinities toward chloride. The association constant dramatically increased when additional hydrogen-bonding sites of two benzamide units were incorporated to the biindolyl scaffold. For example, the association constants of **1a** and **1b** are 5.1×10^3 and 1.4×10^4 M^{-1} in CH_3CN at 22 ± 1 °C, while reference molecule **10** having only two indole NHs showed the association constant of 340 M^{-1} under the same conditions. When the biindolyl backbone was structurally preorganized, the binding affinities toward anions were further increased with additional stabilization energy ($-\Delta\Delta G$) of 2.0 ± 0.2 kcal/mol).

The development of synthetic molecules that can bind and sense an anion is a current topic of much interest in the field of supramolecular chemistry. Hydrogen bonds and electrostatic forces are two key interactions to bind and transport anions in the biological systems such as sulfate- and phosphate-binding proteins[1] and a CIC chloride channel.[2] For example, sulfate binds to the cavity of the sulfate-binding protein by seven hydrogen bonds with peptide backbone NHs and side chains (Ser–OH, Trp–NH) of amino acids.[1a,c] In a CIC chloride channel, chloride was found to be stabilized by multiple hydrogen bonds and electrostatic interactions. Like in the natural system, the polar interactions have been extensively employed in the construction of synthetic receptors that bind anions strongly and selectively.[3] For this purpose, the amido and (thio)ureido groups were most frequently utilized. In addition, the pyrrole and imidazole rings were also used as building blocks for the preparation of anion receptors.

Recently, our group[4] and Beer's group[5] demonstrated that the NHs of 2,2′-biindolyl and indolocarbazole could serve as good hydrogen bond donors. These scaffolds possess two indole NHs capable of simultaneously forming hydrogen bonds with an anion. We here prepared molecular clefts **1** and **2** where additional hydrogen bond donors of two amide NHs were introduced to the 2,2′-biindolyl scaffold to enhance binding affinities toward anions. In addition, the pre-organization effects on the binding event were clearly noticed when the association constants of the biindolyl-based clefts were compared with those of the corresponding indolocarbazole-based ones. Two indole NHs in the latter are conformationally organized to form simultaneous hydrogen bonds with anions, thus leading to much stronger binding affinities.

The syntheses of **1** and **2** are outlined in Scheme 1, and begin with the iodination[6] and Sonogashira coupling reaction[7] of *p*-(*tert*-butyl)aniline (**3**) with trimethylsilylethyne (1 equiv). Then, compound **5** was subjected to oxidative homocoupling[8] followed by double indolization,[9] which afforded 5,5′-di(*tert*-butyl)-7,7′-diiodo-2,2′-biindolyl (**7**). Compound **7** was coupled with *N*-methyl (or *N*-phenyl) 3-ethynylbenzamide (**9a** and **9b**) in the presence of $Pd(dba)_2$/CuI catalyst to give molecular clefts **1a** and **1b**.[10] On the other hand, the reaction of **7** with (dimethylamino)acetaldehyde diethyl acetal[11] in acetic acid afforded a rigid scaffold **8**, which was in turn converted into molecular clefts **2a** and **2b**.[10]

The binding properties were first examined with **1a** and chloride in the ^1H NMR spectroscopy. When tetrabutylammonium chloride (10 equiv) was added to a CD_3CN (0.3 mM) solution of **1a**, the signals of indole NHs and amide NHs were downfield shifted from 10.0 and

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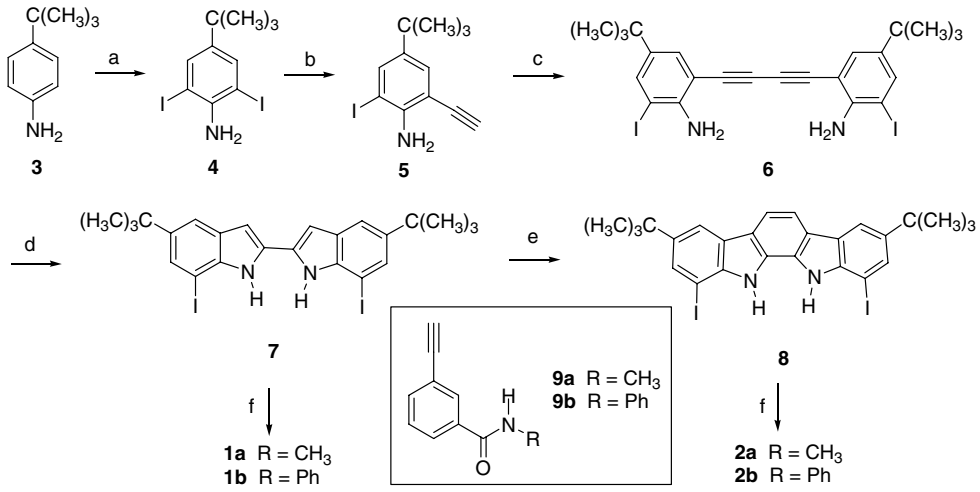
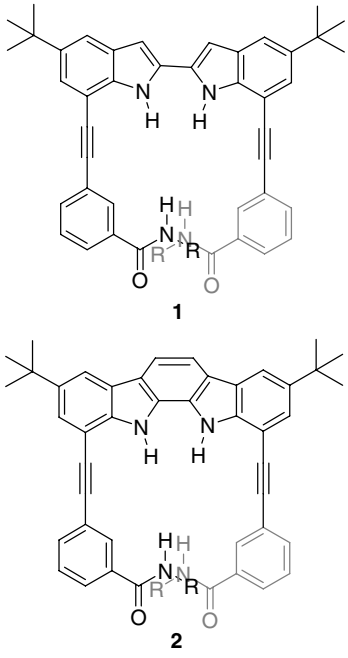


Scheme 1. Syntheses of molecular clefts **1** and **2**. Reagents and conditions: (a) I_2/Ag_2SO_4, EtOH, room temperature, 1 h, 73%; (b) trimethylsilylethyne (1 equiv), $Pd(PPh_3)_2Cl_2$, CuI, THF/Et_3N (v/v 1:1), 50–55 °C, then K_2CO_3/MeOH, room temperature, 30 min, 52% for two steps; (c) $Cu(OAc)_2{\cdot}H_2O$, pyridine, room temperature, 12 h, 90%; (d) CuI, DMF, 110–115 °C, 4 h, 80%; (e) (dimethylamino)acetaldehyde diethyl acetal, CH_3CO_2H, reflux, 2 h, 68%, and (f) **9a** or **9b**, $Pd(dba)_2$, CuI, PPh_3, THF/Et_3N, overnight, 55–60 °C, 62–73%.



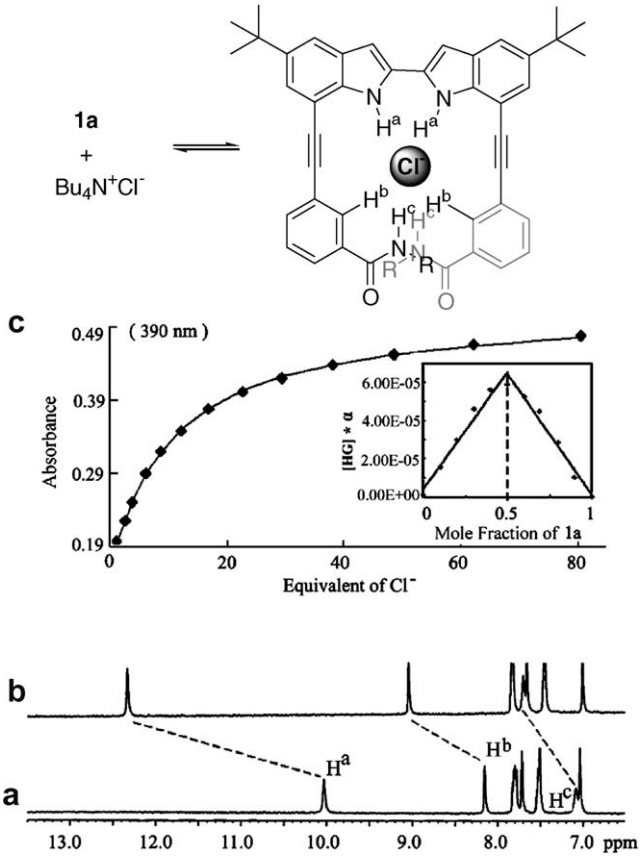


Figure 1. Partial ^1H NMR spectra (500 MHz, CD_3CN) of: (a) **1a** (0.3 mM); (b) **1a** (0.3 mM) + $Bu_4N^+Cl^-$ (3 mM), and (c) a UV–vis titration curve and a Job plot (inset) between **1a** (20 μM) and $Bu_4N^+Cl^-$ in CH_3CN at 22 ± 1 °C.

7.1 ppm to 12.4 and 7.7 ppm, respectively (Fig. 1b). More interestingly, the aryl CH^b signal was also largely shifted from 8.2 to 9.2 ppm. These observations indicate that chloride binds to **1a** by two $CH\cdots Cl^-$ hydrogen bonds as well as four $NH\cdots Cl^-$ hydrogen bonds. The computer modeling shows that all of six hydrogens (two indole NHs, two amide NHs, and two CHs) closely contact with chloride to form hydrogen bonds in the structure of complex **1a**·Cl^- (Fig. 2).

The titration experiment of **1a** with chloride was performed in CH_3CN at 22 ± 1 °C using the UV–vis spectroscopy. The absorption spectrum was gradually changed as a solution of chloride was added while keeping the concentration (2.0×10^{-5} M) of **1a** constant. The association constant was estimated to be 5.1×10^3 M^{-1} by nonlinear least-squares fitting analysis of the titration data (Fig. 1c).[12] The association constant between **1b** and chloride was determined to be 1.4×10^4 M^{-1}, which is slightly higher than that of **1a**. This is possibly attributed to the better hydrogen bond donor of the arylamide

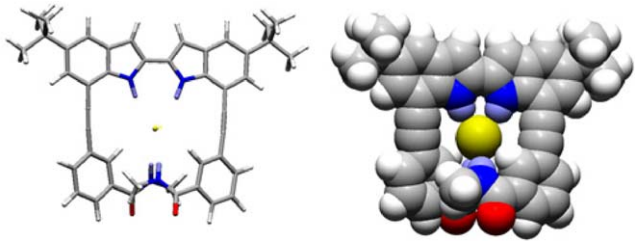


Figure 2. Energy-minimized structures (MacroModel 7.1, MM2* force field)[14] of complex **1a**·Cl^-. Hydrogen bond distances are 2.25 Å for the indole NH···Cl^-, 2.38 Å for the amide NH···Cl^-, and 2.57 Å for the aryl CH···Cl^-.

NHs compared to the alkylamide NHs. As a reference, compound **10** was prepared which bears only two indole NHs, not amide NHs. The association constant between **10** and chloride was found to be 340 M^{-1} under the same conditions. This result clearly supports that the appended amide NHs of **1a** and **1b** participated in the complexation to greatly enhance the association constants. The 1:1 stoichiometry of the complex was in all cases confirmed by the continuous variation (Job) method,[13] and a representative example is shown in Figure 1c (inset).

According to computer modeling,[14] the biindolyl scaffold exists in a *s-trans* conformation, two indole NHs being in an opposite direction, to minimize dipole–dipole repulsion. When complexed, however, it adopts a *s-cis* conformation to simultaneously form hydrogen bonds with chloride (Fig. 3). This structural reorganization on the binding process decreases the binding energy in terms of both enthalpy and entropy. With this in mind, we synthesized a rigid scaffold **8** where two indoles are bridged with ethyno group at 3,3′ position to be directed to the same side. Molecular clefts **2a** and **2b** were prepared by incorporating two benzamide units to this scaffold, just like in **1a** and **1b**. The association constants of **2a** and **2b** with chloride were found to be 1.1×10^5 and 3.7×10^5 M^{-1}, respectively, in CH_3CN at 22 ± 1 °C.

Next, the binding properties of two representative clefts **1a** and **2a** were revealed with other common anions and the association constants were compared with each other. As summarized in Table 1, the association constants of both **1a** and **2a** increase in the order of $CH_3CO_2^- > Cl^- > Br^- > HSO_4^- > I^-$, as anticipated from mainly electrostatic nature of hydrogen-bonding interaction. Furthermore, the conformationally preorganized cleft **2a**, compared to **1a**, shows consistently higher binding affinities toward all anions examined here. The relative ratios of the association constants are in the range of 20–40, reflecting that the pre-organization in **2a** results in gaining additional stabilization energy ($-\Delta\Delta G$) of 2.0 ± 0.2 kcal/mol.

In conclusion, molecular clefts were synthesized as a new class of anion receptors based on hydrogen bonds. The binding affinities greatly increased up to 40-folds when additional hydrogen-bonding sites were introduced in a convergent manner. The binding affinities further increased by the conformational pre-organization of the biindolyl backbone. By the variation of the appended amide units, we are currently focusing on the development of functional molecular clefts such as a colorimetric chemosensor and a transporter of an anion through biological membrane.

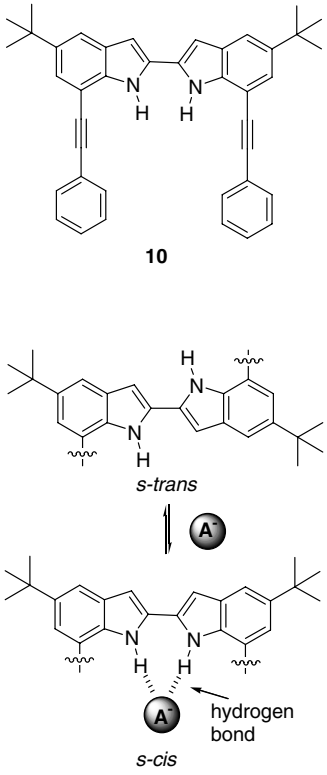


Figure 3. Conformational switch of biindolyl scaffold when complexed with an anion, chloride.

Table 1. Association constants (K_a ± 20%, M^{-1}) of clefts **1a** and **2a** and anions in CH_3CN at 22 ± 1 °C[a]

Anion	K_a (M^{-1})		Ratio K_a (**1a**)/K_a (**2a**)
	1a	**2a**	
Cl^-	5.1×10^3	1.1×10^5	22
Br^-	2.1×10^2	8.7×10^3	41
I^-	6[b]	1.8×10^2	30
HSO_4^-	77	2.1×10^3	27
$CH_3CO_2^-$[c]	1.4×10^5	$>2 \times 10^6$	—

[a] Titration experiments were all duplicated in UV–vis spectroscopy, in which the concentration of **1a** (or **2a**) remains constant (2.0×10^{-5} M) throughout each titration and anions were used as tetrabutylammonium salts.

[b] The association constant between **1a** and I^- was evaluated in the ^1H NMR spectroscopy.

[c] The association constants of **1a** and **2a** with acetate were determined in 10% (v/v) DMSO/CH_3CN.

Acknowledgements

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10. Physical properties and spectral data of molecular clefts.
Compound **1a**: mp 240–241 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.52 (s, 2H; NH), 8.59 (s, broad, 2H; NH), 8.20 (s, 2H), 7.88 (d, $J = 7.6$ Hz, 4H), 7.65 (s, 2H), 7.57 (t, $J = 7.6$ Hz, 2H), 7.41 (s, 2H), 7.18 (s, 2H), 2.81 (d, $J = 4.4$ Hz, 6H), 1.38 (s, 18H); ^{13}C NMR (400 MHz, DMSO-d_6): δ (ppm) 166.5, 143.0, 135.9, 135.5, 134.5, 132.5, 130.7, 129.3, 129.3, 127.7, 124.3, 123.6, 118.2, 105.1, 101.5, 92.6, 88.2, 34.9, 32.2, 26.9; Anal. Calcd for $C_{44}H_{42}N_4O_2$: C, 80.21; H, 6.43; N, 8.50. Found: C, 80.22; H, 6.42; N, 8.49; HRMS-FAB (m/z) $[M]^+$ calcd for $C_{44}H_{42}N_4O_2$ 658.3308; found 658.3295.
Compound **1b**: mp 222–223 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.52 (s, 2H; NH), 10.38 (s, 2H; NH), 8.33 (s, 2H), 7.97 (t, $J = 7.6$ Hz, 4H), 7.81 (d, $J = 7.6$ Hz, 4H), 7.66 (d, $J = 1.2$ Hz, 2H), 7.63 (t, $J = 7.8$ Hz, 2H), 7.44 (d, $J = 2.0$ Hz, 2H), 7.37 (t, $J = 8.0$ Hz, 4H), 7.20 (d, $J = 2.0$ Hz, 2H), 7.12 (t, $J = 7.4$ Hz, 2H), 1.38 (s, 18H); ^{13}C NMR (400 MHz, DMSO-d_6): δ (ppm) 164.8, 142.4, 139.0, 135.4, 135.3, 134.4, 131.9, 130.6, 128.9, 128.6, 123.8, 123.1, 120.4, 104.5, 101.0, 93.2, 91.9, 75.7, 51.9, 34.3, 33.3, 31.6, 30.s7; Anal. Calcd for $C_{54}H_{46}N_4O_2$: C, 82.84; H, 5.92; N, 7.16. Found: C, 82.86; H, 5.93; N, 7.17; HRMS-FAB (m/z) $[M]^+$ calcd for $C_{54}H_{46}N_4O_2$ 782.3621; found 782.3624.
Compound **2a**: mp 245–246 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.13 (s, 2H; NH), 8.60 (m, 2H; NH), 8.31 (d, $J = 1.6$ Hz, 2H), 8.20 (s, 2H), 8.05 (s, 2H), 7.92–7.88 (m, 4H), 7.66 (d, $J = 1.6$ Hz, 2H), 7.63 (t, $J = 7.6$ Hz, 2H), 2.80 (d, $J = 8.0$ Hz, 6H), 1.45 (s, 18H); ^{13}C NMR (400 MHz, DMSO-d_6) δ (ppm) 166.3, 142.7, 138.2, 135.6, 134.5, 130.7, 129.6, 128.0, 126.4, 126.1, 124.4, 123.2, 121.3, 118.4, 113.0, 104.7, 92.9, 87.6, 35.1, 32.3, 31.3; Anal. Calcd for $C_{46}H_{42}N_4O_2$: C, 80.91; H, 6.20; N, 8.20. Found: C, 80.91; H, 6.21; N, 8.21; HRMS-FAB (m/z) $[M]^+$ calcd for $C_{46}H_{42}N_4O_2$ 682.3308; found 682.3311.
Compound **2b**: mp 227–228 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.54 (s, 2H; NH), 10.52 (s, 2H; NH), 8.34 (s, 2H), 8.32 (d, $J = 1.6$ Hz, 2H), 8.05 (s, 2H), 7.94–7.98 (m, 4H), 7.79 (d, $J = 1.6$ Hz, 2H), 7.77 (s, 2H), 7.68 (d, $J = 1.6$ Hz, 2H), 7.62 (t, $J = 7.8$ Hz, 2H), 7.33 (t, $J = 8.0$ Hz, H), 7.10 (t, $J = 7.4$ Hz, 2H), 1.45 (s, 18H); ^{13}C NMR (400 MHz, DMSO-d_6): δ (ppm) 165.2, 142.7, 139.6, 138.3, 136.1, 134.9, 131.2, 130.1, 129.7, 129.2, 128.7, 126.4, 126.1, 124.7, 123.9, 121.3, 121.6, 118.5, 113.0, 104.7, 92.9, 87.9, 35.1, 33.3; Anal. Calcd for $C_{56}H_{46}N_4O_2$: C, 83.35; H, 5.75; N, 6.94. Found: 83.34; H, 5.77; N, 6.94; HRMS-FAB (m/z) $[M]^+$ calcd for $C_{56}H_{46}N_4O_2$ 806.3621; found 806.3630.
Compound **10**: mp 219–220 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.46 (s, 2H; NH), 7.77 (d, $J = 2.0$ Hz, 2H), 7.75 (d, $J = 1.6$ Hz, 2H), 7.62 (d, $J = 1.6$ Hz, 2H), 7.46–7.51 (m, 6H), 7.39 (d, $J = 2.0$ Hz, 2H), 7.16 (d, $J = 2.0$ Hz, 2H), 1.37 (s, 18H); ^{13}C NMR (400 MHz, DMSO-d_6): δ (ppm) 143.0, 135.8, 132.4, 132.4, 132.4, 132.2, 129.2, 124.1, 123.5, 123.5, 117.9, 105.4, 101.4, 93.2, 97.6, 34.9, 32.2; Anal. Calcd for $C_{40}H_{36}N_2$: C, 88.20; H, 6.66; N, 5.14. Found: C, 88.20; H, 6.64; N, 5.13; HRMS-FAB (m/z) $[M]^+$ calcd for $C_{40}H_{36}N_2$ 544.2878; found 544.2880.
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14. The modeling study was carried out using MM2* 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.