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# A catenated anion receptor based on indolocarbazole

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ABSTRACT

A catenated anion receptor **7** comprising two indolocarbazole units was prepared by olefin ring-closing metathesis using Grubbs' catalyst. Receptor **7** possesses a cage-like cavity where anions are encapsulated by forming four hydrogen bonds in the order of $Cl^- > AcO^- > N_3^- > H_2PO_4^- > Br^- > HSO_4^- > I^- \approx NO_3^-$ in 1% $H_2O$/acetone.

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Interlocked molecules such as catenanes and rotaxanes have been intensively studied over the past two decades to develop molecular-level machines and devices.[1] The syntheses of these molecules have been successfully achieved by utilizing external templates such as metal cations. In recent years, Beer and coworkers have nicely demonstrated that anions can also serve as effective templates for the preparation of pseudorotaxanes, rotaxanes, and catenanes.[2,3] Moreover, the anionic templates can be easily removed to give interlocked molecules with empty sites for anion binding, reminiscent of imprinted polymers. Due to the interlocked nature of the two molecular components, these receptors are able to bind anions with high stability and selectivity compared to the corresponding 2:1 complexes.

Indolocarbazole derivatives with two preorganized NH protons have been used as versatile building blocks for the construction of anion receptors. Beer and coworkers reported for the first time that indolocarbazoles strongly bound anions by two hydrogen bonds in acetone.[4] Utilizing this scaffold, the same group described a variety of anion-binding interpenetrated and interlocked structures.[2,3,5] Our group has also employed indolocarbazole derivatives in the preparation of molecular clefts, macrocycles, and foldamers that bind anions with high affinities and selectivity in organic solvents or in water.[6] Herein, we prepared for the first time an indolocarbazole-based catenane **7** which contains a cage-type cavity with four NH protons capable of hydrogen bonding with an anion. Among the anions examined here, receptor **7** binds chloride most strongly with an association constant ($K_a$) of $1.4 \times 10^5\ M^{-1}$ in 1% $H_2O$/acetone.

The synthesis of **7** is outlined in Scheme 1. Mono-allylation (48% yield) of triethylene glycol (**1**) followed by bromination (90% yield) afforded compound **2**. The substitution reaction of **2** with 4-bromophenol/$K_2CO_3$ gave compound **3** (90% yield) which was converted into boronic acid **4** in 87% yield.[7] On the other hand, an indolocarbazole **5** was prepared from 4-aminobenzoic acid according to the procedures described previously.[6] The Suzuki coupling of **4** and **5** provided compound **6** in 58% yield.[8] Ring-closing metathesis[9] of **6** with Grubb's catalyst was carried out in the presence of tetrabutylammonium chloride (0.5 equiv) to give a mixture of cyclic products which was directly subjected to catalytic hydrogenation ($H_2$, Pd/C) to yield the desired receptor **7** (26% yield for two steps),[10] together with a monocyclic product **8** (14% yield for two steps)[10] used as a reference molecule. Here, the yield of **7** was slightly lower in the absence of tetrabutylammonium chloride, but the reaction conditions were not optimized.

$^1$H NMR spectra of **7** and **8** are similar to each other in chemical shifts and splitting patterns, but there are two important differences. First, the chemical shift of the NH protons of **7** is 10.5 ppm in $CDCl_3$ at room temperature while that of **8** is 9.6 ppm under the same conditions. This downfield shift ($\Delta\delta = 0.9$ ppm) in **7** is possibly attributed to intramolecular hydrogen bonds between the indole NHs of one ring and the phenolic oxygen atoms of the other, as demonstrated by computer modeling (Fig. 1a). Second, the aromatic proton ($H^a$) in the phenolic arms of **7** appears as a broad singlet at 7.0 ppm without splitting, while that of **8** resonances at 7.2 ppm as a well-resolved sharp doublet ($J = 8.4$ Hz). These observations agree well with the stacked arrangement of four phenolic rings in the energy-minimized structure of **7** (Fig. 1), which may interfere with the free rotation of the phenolic C–O bond, thus giving rise to signal broadening. In addition, the ring current of stacked aromatic rings must be responsible for the upfield shift ($\Delta\delta = -0.2$ ppm) of the $CH^a$ signal of **7** relative to that of reference **8**. Together with $^1$H NMR observations mentioned here, mass spectroscopy clearly supports the structure of catenane **7** ($m/z$ for $C_{128}H_{164}N_4O_{24}$ calcd 2142.17, found 2142.10).

The binding properties of **7** with anions were revealed in 1% (v/v) $H_2O$/acetone at 24 ± 1 °C using $^1$H NMR and fluorescence spectroscopy. Addition of chloride ion as a tetrabutylammonium salt gave a new set of $^1$H NMR signals corresponding to the chloride complex of **7** (Fig. 2). The $^1$H NMR signals of the complex increase at the expense of unbound signals with increasing the amount of chloride. In the complex, the NH signal was largely downfield

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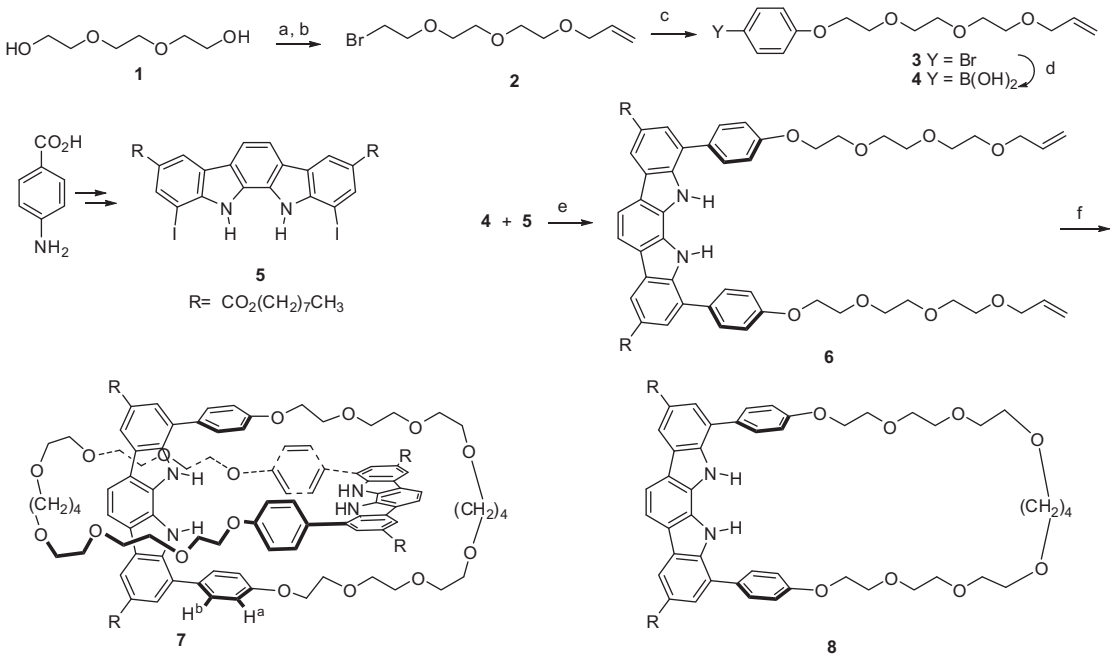


**Scheme 1.** Synthesis of **7** and **8**. Reagents and conditions: (a) allyl bromide, *t*-BuOK, THF, rt, 48%; (b) $CBr_4$, THF, rt, 85%; (c) 4-bromophenol, $K_2CO_3$, DMF, 80–84 °C, 90%; (d) $B(OMe_3)_3$, *n*-BuLi, TMEDA, THF, −78 °C to rt, 87%; (e) $Pd(PPh_3)_4$, saturated aqueous $Na_2CO_3$, DME, 80–82 °C, 58%; (f) Grubb's first catalyst, TBACl (0.5 equiv), $CH_2Cl_2$, rt, then Pd/C, $H_2$, EtOAc, **7** (25% yield for two steps) and **8** (14% yield).

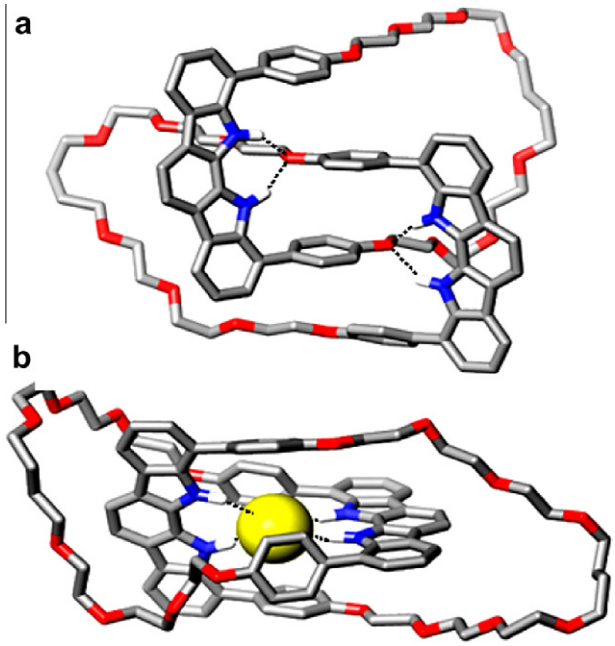


**Figure 1.** Energy-minimized structures (MacroModel 9.1, MMFFs force field, in $CHCl_3$) of (a) unbound **7** and (b) complex **7**·$Cl^-$ where the ester side chains are replaced by hydrogen atoms. Hydrogen bonds are shown as dotted lines, and hydrogen atoms except NH protons are omitted for clarity.

shifted by $\Delta\delta$ = ~2 ppm as a result of hydrogen bonds. Moreover, the $CH^a$ signal becomes sharpened, suggesting that anion binding may lock the rotation of the phenolic ring. It should be mentioned that reference **8** afforded time-averaged signals upon binding the chloride ion under the same conditions. As shown in Figure 1b, the energy-minimized structure of complex **7**·$Cl^-$ demonstrates that the chloride ion is encapsulated in the cavity surrounded by four phenolic planes by simultaneously forming four hydrogen bonds with the convergent indole NHs.

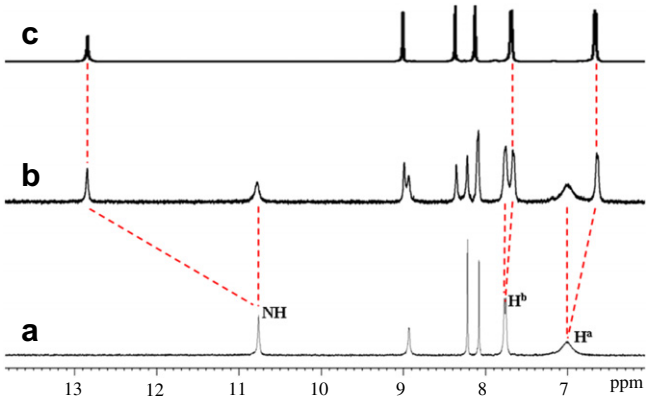


**Figure 2.** Partial $^1H$ NMR spectra (400 MHz, 1% $H_2O$/acetone-$d_6$, rt) of **7** in the presence of $Bu_4N + Cl^-$: (a) 0, (b) ~0.5 equiv, and (c) 1 equiv.

The association constants between **7** and anions were determined by fluorescence titrations in 1% (v/v) $H_2O$/acetone at 24 ± 1 °C (Fig. 3). Excitation of the indolocarbazole unit at 350 nm gave rise to an emission band in between 470 nm and 550 nm, showing the maximum intensity at 404 nm. Unlike most anion receptors showing fluorescent quenching by anion binding, receptor **7** displays an enhancement upon anion binding. As a representative example, the emission increases by approximately threefold when tetrabutylammonium chloride (~6 equiv) was added to a solution of **7** ($1.0 \times 10^{-5}$ M). The association constants ($K_a$'s) were estimated by nonlinear least squares fitting analysis[11] with a 1:1 binding isotherm, and the results are summarized in Table 1. Job's plots[12] proved 1:1 binding modes of **7** with all anions. The chloride ion binds to **7** most strongly with the association constant of $1.4 \times 10^5$ $M^{-1}$ which is approximately 20-fold higher than that ($7.3 \times 10^3$ $M^{-1}$) of **8** with chloride under the same conditions, suggesting that four indole NHs of **7** simultaneously participate in hydrogen bonding with the same chloride. The magnitudes of the

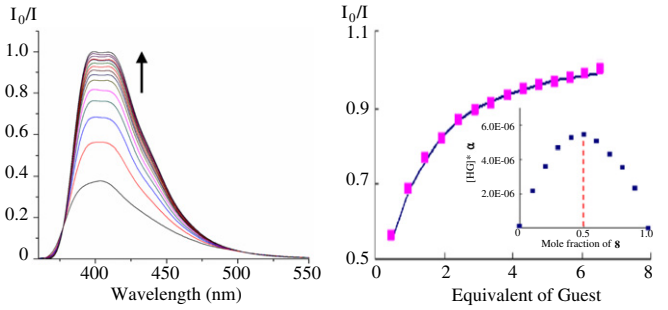


**Figure 3.** (a) Fluorescence spectral changes (excitation: 350 nm) of **7** ($1.0 \times 10^{-5}$ M in 1% $H_2O$/acetone-$d_6$) upon addition of $Bu_4N^+Cl^-$ at 24 ± 1 °C, (b) experimental (filled squares) and theoretical plots of titration curves and Job's plot (inset).

**Table 1**
Association constants ($K_a$ ± 15%, $M^{-1}$) of **7** with anions in 1% (v/v) $H_2O$/acetone at 24 ± 1 °C[a]

| Anion[a] | $K_a$ ($M^{-1}$) | $\Delta G$ (kcal/mol) |
|---|---|---|
| $Cl^-$ | 140,000 | 7.00 |
| $Br^-$ | 660 | 3.83 |
| $I^-$ | —[b] | — |
| $AcO^-$ | 71,000 | 6.59 |
| $H_2PO_4^-$ | 5700 | 5.11 |
| $N_3^-$ | 30,000 | 6.09 |
| $HSO_4^-$ | 130 | 2.87 |
| $NO_3^-$ | —[b] | — |

[a] Titrations were at least duplicated, and anions were used as tetrabutylammonium salts.
[b] Too small to be determined.

association constants are in the order of $Cl^- > AcO^- > N_3^- > H_2PO_4^- > Br^- > HSO_4^- > I^- \approx NO_3^-$, indicative of the binding affinities depending on both the shape and basicity of anions.

In conclusion, a catenane-based anion receptor **7** has been synthesized utilizing an indolocarbazole scaffold that possesses two indole NHs capable of forming strong hydrogen bonds with anions. Among anions, the spherical chloride ion binds most strongly in the cage-like cavity of **7** by four hydrogen bonds. Owing to the interlocked nature, the exchange process between the unbound and the complex was found to be slow on the $^1$H NMR time scale, demonstrating that catenane-based anion receptors increase not only the thermodynamic stability of the complex but also the kinetic stability.

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10. *Spectroscopic data of* **7**: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 10.50 (s, 2H, NH), 8.88 (s, 4H), 8.13 (s, 4H), 8.08 (s, 4H), 7.63 (br, 8H), 6.84 (br, 8H), 4.29 (m, 4H), 3.50–3.25 (m. 8H), 1.78–1.26 (m, 48H), 0.87 (m, 12H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 163.4, 158.4, 140.4, 130.7, 129.8, 126.6, 125.7, 125.1, 124.5, 123.0, 121.9, 121.2, 114.9, 113.1, 77.2, 70.9, 70.7, 70.6, 69.9, 69.4, 67.0, 65.3, 31.8, 29.2, 29.1, 28.8, 26.1, 22.6, 14.1; IR (thin film) 3375, 3052, 2921, 2856, 1708, 1663, 1610, 1556 cm$^{-1}$; MALDI-TOF ($m/z$) [M]+ calcd for $C_{128}H_{164}N_4O_{24}$ 2141; found 2142.10. *Spectroscopic data of* **8**: $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ (ppm): 9.57 (s, 2H, NH), 8.85 (s, 2H), 8.09 (s, 4H), 7.62 (d, 4H, $J$ = 8.8 Hz), 7.17 (d, 4H, $J$ = 8.4 Hz), 4.40 (m, 4H), 4.30 (m, 4H), 3.93 (m, 4H), 3.67–3.47 (m, 32H), 1.77–1.26 (m, 24H), 0.86 (m, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ (ppm) 168.0, 158.0, 139.6, 129.9, 128.8, 125.9, 125.3, 124.4, 124.0, 121.4, 120.8, 114.5, 112.8, 70.6, 70.2, 69.6, 69.0, 66.8, 64.8, 31.3, 28.8, 28.7, 28.2, 25.9, 22.1, 13.6; IR (thin film) 3371, 2929, 2856, 1704, 1663, 1610, 1561 cm$^{-1}$; MALDI-TOF ($m/z$) [M]+ calcd for $C_{64}H_{82}N_2O_{12}$ 1071; found 1071.95.
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