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Synthesis of Biindole−Diazo Conjugates as a Colorimetric Anion Receptor

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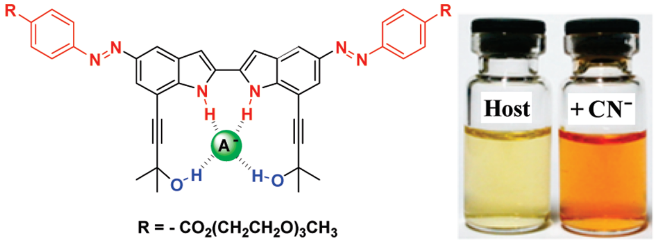
ABSTRACT



A colorimetric anion receptor based on an indole scaffold has been synthesized by incorporating an azobenzene chromophore to the 5-position of indole. The receptor binds anions by hydrogen bonds which are effectively transmitted through resonance to the chromophore to give rise to color changes. The cyanide ion induced a pronounced color change from light yellow to reddish orange, but less intense or negligible changes were observed with the other anions examined here.

Anions play crucial roles in many chemical and biological processes, which inspire supramolecular chemists to design and synthesize a variety of anion receptors.[1,2] The binding event has been analyzed by many spectroscopic techniques that display characteristic absorption, emission, or electrochemical signals before and after the formation of the corresponding receptor−anion complexes. Visual detection is simple and convenient, not requiring expensive instruments, and is highly desirable for applications in rapid screening processes and in environmental field work.[3]

In recent years, we and others have prepared a variety of indole-based anion receptors including oligoindole foldamers, macrocycles, and molecular clefts.[4−9] These receptors strongly bind anions by hydrogen bonds, but only a few of them display color changes upon anion binding.[10] For example, Sessler et al. prepared 3-diindol-3-yl quinoxalines which showed a distinct color change from yellow to brown or orange upon binding fluoride or dihydrogen phosphate.[10d] Shiraishi et al. synthesized a bisindolyl molecule that exhibited noticeable changes in color and fluorescence in the presence of excess fluoride.[10e]

Herein, we report for the first time the synthesis of a biindole−diazo conjugate **10** that has been further utilized to prepare a colorimetric anion receptor **11**. In the presence of relatively basic anions such as fluoride, acetate, dihydrogen

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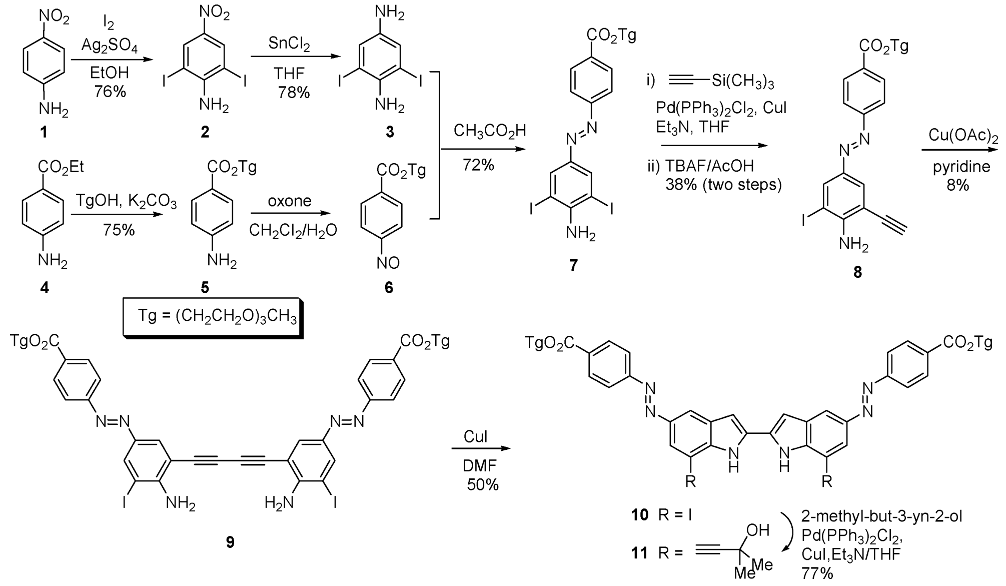
Scheme 1. Synthesis of **11**



phosphate, and cyanide, compounds **10** and **11** display noticeable color changes from pale yellow to orange or reddish orange due to the formation of hydrogen bonds or deprotonation in 10% (v/v) DMSO/CH_3CN.

In general, colorimetric receptors consist of binding and signaling subunits that are electronically conjugated to each other to effectively induce color changes. In this context, the chromogenic diazo unit is introduced at the 5-position of indole to achieve direct resonance between them.[11] As shown in Figure 1, the electron-withdrawing ester group at the end increases not only the degree of π-conjugation but also the hydrogen bond donor ability of the indole NH.

The synthesis of biindole−diazo conjugates **10** and **11** began with 4-nitroaniline (**1**) (Scheme 1). Compound **1** was reacted with I_2/Ag_2SO_4[12] to give 2,6-diiodo-4-nitroaniline (**2**, 65% yield), which was reduced with $SnCl_2{\cdot}2H_2O$ to give 2,6-diiodobenzene-1,4-diamine (**3**, 82% yield). On the other hand, nitroso compound **6** was prepared from ethyl 4-aminobenzoate (**4**) via two steps: transesterification (52% yield) and oxidation with oxone. **6** was then directly used for the next reaction without further purification. Condensation of **3** and **6** gave a diazobenzene derivative **7** in 69% yield.[13] The Sonogashira coupling reaction[14] of **7** with 1-trimethylsilylethyne (1 equiv), followed by a protic desilylation with Bu_4NF (1.1 equiv) and CH_3COOH (1.1 equiv), afforded **8** in 45% yield (two steps). **8** was sequentially subjected to Glaser-type oxidative homocoupling[15] (93% yield) and cyclization in the presence of copper iodide[16] (50% yield)

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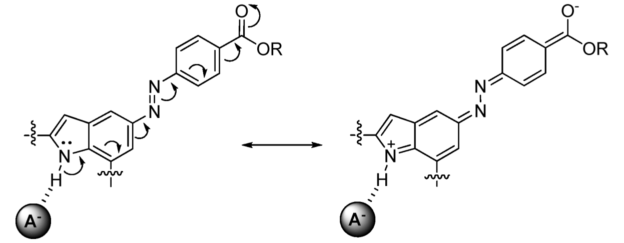

Figure 1. Resonance structures of indole−diazo scaffold.

to give a biindole−diazo conjugate **10**. Finally, **11** was obtained in 76% yield by the Sonogashira reaction of **10** and 2-methylbut-3-yn-2-ol.

We first examined anion-induced color changes of **10** and **11** in 10% (v/v) DMSO/CH_3CN. Compound **10** displays noticeable color changes from pale yellow to orange or reddish orange upon addition (5 equiv) of fluoride, acetate, dihydrogen phosphate, and cyanide (Figure 2). Other anions such as chloride, bromide, iodide, azide, nitrate, and hydrogen sulfate caused no change in color. These observations are consistent with changes in UV−visible absorption spectra. Addition of relatively basic anions such as F^-, AcO^-, $H_2PO_4^-$, and CN^- to **10** increases the absorption (λ_{max} 480 nm) between 440 and 560 nm,[17] but negligible changes were observed with other anions.

Anions are hydrogen bonded tighter to the NHs in **10**, optimizing the interactions because it possesses only two hydrogen bond donors of indole NHs. On the other hand, **11** contains two additional OH donors and therefore anions may be situated in the middle of four donors in a way to maximize total hydrogen bonding interactions. As a result, perturbation of the indole N−H bonds by anion binding in **11** is presumably weaker than that in **10**, which may be responsible for smaller changes in color and absorption spectra of **10**. It should be mentioned that addition of tetrabutylammonium hydroxide to **10** and**11** yielded a new strong band between 440 and 560 nm (Supporting Information), similar to those observed with cyanide. This suggests that the inherent basicity of cyanide ion is responsible for the most pronounced changes by causing deprotonation of the indole NHs under the given conditions.[18]

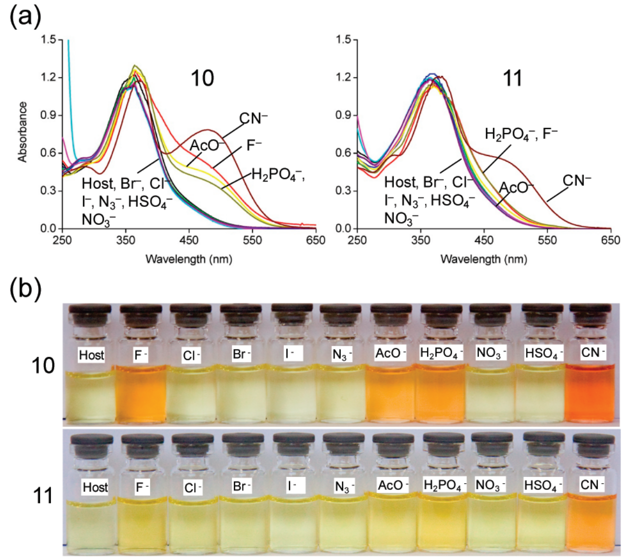

Figure 2. UV/vis spectra (a) and color changes (b) of **10** (2.0×10^{-5} M) and **11** (2.0×10^{-5} M) in the presence of various anions (5 equiv) in 1:9 (v/v) DMSO/CH_3CN.

Table 1. Association Constants (K_a, M^{-1}) of **10** and **11** with Anions in DMSO/CH_3CN (v/v, 1:9) at 25 ± 1 °C[a]

	association constant (K_a, M^{-1})		
anion	**10**	**11**	ratio of **11**/**10**
F^-	–[b]	200 000	
Cl^-	57	8 900	156
Br^-	<5	1 300	>260
I^-	<5	<5	
N_3^-	120	330	3
$CH_3CO_2^-$	–[b]	77 000	
$H_2PO_4^-$	–[b]	40 000	
NO_3^-	<5	59	>12
HSO_4^-	<5	56	>11

[a] Titrations were duplicated by ^1H NMR (Cl^-, Br^-, I^-, N_3^-, NO_3^-, HSO_4^-) or UV/vis spectroscopy (F^-, AcO^-, $H_2PO_4^-$), using tetrabutylammonium salts of anions, and errors in K_a values were within 20%. [b] Association constants for these anions could not be estimated because the binding process competes with deprotonation under the titration conditions.[17]

The association constants (K_a, M^{-1}) of **10** and **11** with anions were determined by either ^1H NMR or UV−visible titraions. Upon addition of anions as their tetrabutylammonium salts in 9:1 (v/v) CD_3CN/DMSO-d_6, the ^1H NMR signal of NHs was considerably downfield ($\Delta\delta$ up to 1.2 ppm), while the aromatic CH signals were slightly upfield shifted ($\Delta\delta \approx 0.1$ ppm) (Figure 3). These observations are consistent with the formation of hydrogen bonds between the indole NHs and anions. In addition, UV−visible titrations showed clear isosbestic points, indicative of two species being in

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(17) Upon addition of basic anions F^-, AcO^-, and $H_2PO_4^-$, ^1H NMR signals for the NHs of **10** disappeared in 10% (v/v) d_6-DMSO/CD_3CN at room temperature. When a solution containing **10** and each anion (1.5 equiv) was cooled to −40 °C, the signal for HF_2^- appeared at 16.3 ppm as a triplet, indicative of deprotonation. In cases of AcO^- and $H_2PO_4^-$, the NH signals of the corresponding complexes could be seen at 12.9 and 11.9 ppm, respectively (Supporting Information). In addition, the UV−visible spectra (Figure 2a and Supporting Information) show a new absorption band (λ_{max} 480 nm) corresponding to deprotonation but the absorption intensities are considerably weaker compared to those obtained with OH^- and CN^-. These results suggest that both processes of binding and deprotonation occur and compete with each other under the given conditions.

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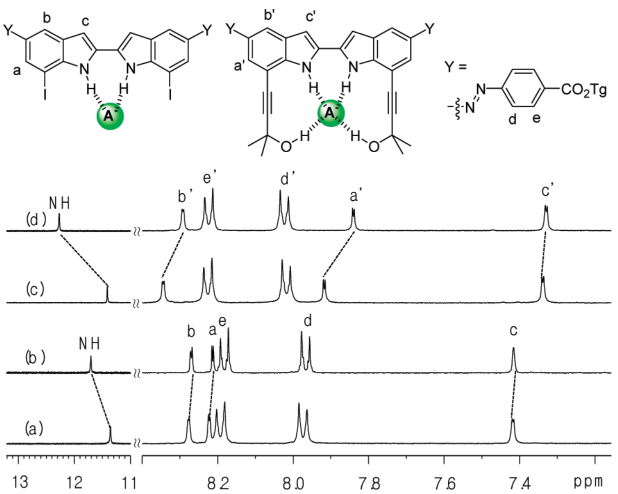

Figure 3. Proposed molecular structures of complexes (top) and partial ^1H NMR spectra (bottom) (400 MHz, 10% DMSO-d_6/CD_3CN, 25 °C) of (a) **10** (1.0 mM), (b) **10** + TBACl (5 equiv), (c) **11** (1.0 mM), and (d) **11** + TBACl (5 equiv)

equilibrium. The titration curves were all analyzed by the nonlinear curve fitting method[19] and fitted to a 1:1 binding isotherm. Job's plots[19b] also support 1:1 stoichiometries of complexes (Supporting Information). From the association constants summarized in Table 1, two trends are apparent. First, basic anions bind more strongly to **10** and **11**, as commonly seen in anion receptors based on hydrogen bonding interactions. Second, **11** shows much higher affinities than **10** by up to 2 orders of magnitude, suggesting that the two additional hydroxyl groups are simultaneously involved in hydrogen bonding with the anion.

In summary, we synthesized a biindole−diazo conjugate **10** that can be used as a useful building block for the construction of colorimetric anion receptors. By using this scaffold, anion receptor **11** has been prepared which strongly binds anions by four hydrogen bonds and produces a color change. Incorporation of the colorimetric unit **10** to foldamers and macrocycles may afford molecular probes and materials that can produce characteristic visual signals upon applying anionic stimulation.

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Supporting Information Available: Synthesis and characterization of new compounds and binding studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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