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Fine tuning of receptor polarity for the development of selective naked eye anion receptor

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ABSTRACT

We designed and synthesized new anion receptors **1**, **2**, and **3**, which have different N–H polarity. According to their N–H polarities, these receptors showed different selectivities for the anions they were interacting with. The difference of selectivity could be easily recognized from their color change during recognition events. Therefore, fine tuning of receptor polarity could be a good strategy for the designing of a selective anion receptor and made it possible to develop a selective naked eye anion receptor.

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The design and synthesis of receptors capable of binding and sensing anions selectively have drawn considerable attention because anions play a major role in biological, medical, environmental, and chemical sciences.[1] Many chemical sensors follow the approach of the covalent attachment of signaling subunits and binding sites.[2] Chromogenic or fluorogenic groups that are covalently linked to the receptor moiety as signaling subunits and multiple hydrogen-bonding interactions as binding sites have been utilized in this regard. For binding sites, molecules containing polarized N–H fragments are widely used as receptors for recognition and sensing purposes in aprotic solvents, such as $CHCl_3$, MeCN, and DMSO. Polarized N–H groups, behaving as H bond donors to the anions, typically used in chromogenic or fluorogenic chemosensors are ureas,[3] thioureas,[4] pyrroles,[5] amines[6] and amides.[7]

When designing an anion receptor, the N–H fragment of a receptor can be further polarized through the insertion onto the molecular framework of the electron-withdrawing substituent and its H-bond donor tendencies increased. Furthermore, extreme polarization may lead to deprotonation from the receptor. On deprotonation, a substantial delocalization of negative charge usually leads to a large red shift, which results in drastic color changes of solution. In consequence, naked detection of the anion becomes possible.[8] Therefore, fine tuning of polarity of the N–H fragment could lead to development of selective naked eye anion receptor.

Previously, we reported on novel colorimetric receptor **1**, which had a nitrophenyl group and a quinoline group as chromogenic signaling subunits.[9] In this receptor, one amide and one amine group is incorporated so that anions can make strong multiple hydrogen bonding with the hydrogen atoms of these groups and we found that the receptor **1** binds anions with a selectivity of $F^- > CN^- > CH_3CO_2^-$ and proved to be an efficient naked-eye detector for the fluoride and cyanide ion in acetonitrile.

As an extension of our work, we have designed new receptors **2** and **3**. The new receptor **2** has only amide groups and the new receptor **3** has only amine groups for hydrogen-bonding. Our intention was to compare the anion detection abilities of the receptors **1**, **2**, and **3**, which have different N–H polarities, and we found that these receptors detect anions through hydrogen bonding and deprotonation.

The synthesis of the receptor **1** was previously reported.[9] Receptor **2** was synthesized by the reaction of oxalyl chloride, 4-nitroaniline, and 8-aminoquinoline. From the mixture of the compounds **2**, **4**, and **5** the compounds **2** and **4** were precipitated as an inseparable mixture while the compound **5** was soluble. After the mixture of **2** and **4** was filtered, the mixture of **2** and **4** was treated with di-*tert*-butyl dicarbonate to give BOC protected compounds and the compound **6** could be separated through silica gel chromatography. Removing BOC group with TFA gave the desired compound **2** in 9.8% yield for the three step reactions. The receptor **3** was synthesized from the reduction of the compound **1** with borane dimethyl sulfide complex in 46% yield (Scheme 1).[10]

As the compound **2** was soluble only in DMSO, we compared the binding abilities of three receptors **1**, **2**, and **3** in DMSO.

The receptors **1** and **2** displayed strong absorption bands at 333 and 334 nm in DMSO, respectively. Figure 1a and b show the family of spectra obtained over the course of the titration of solutions **1**

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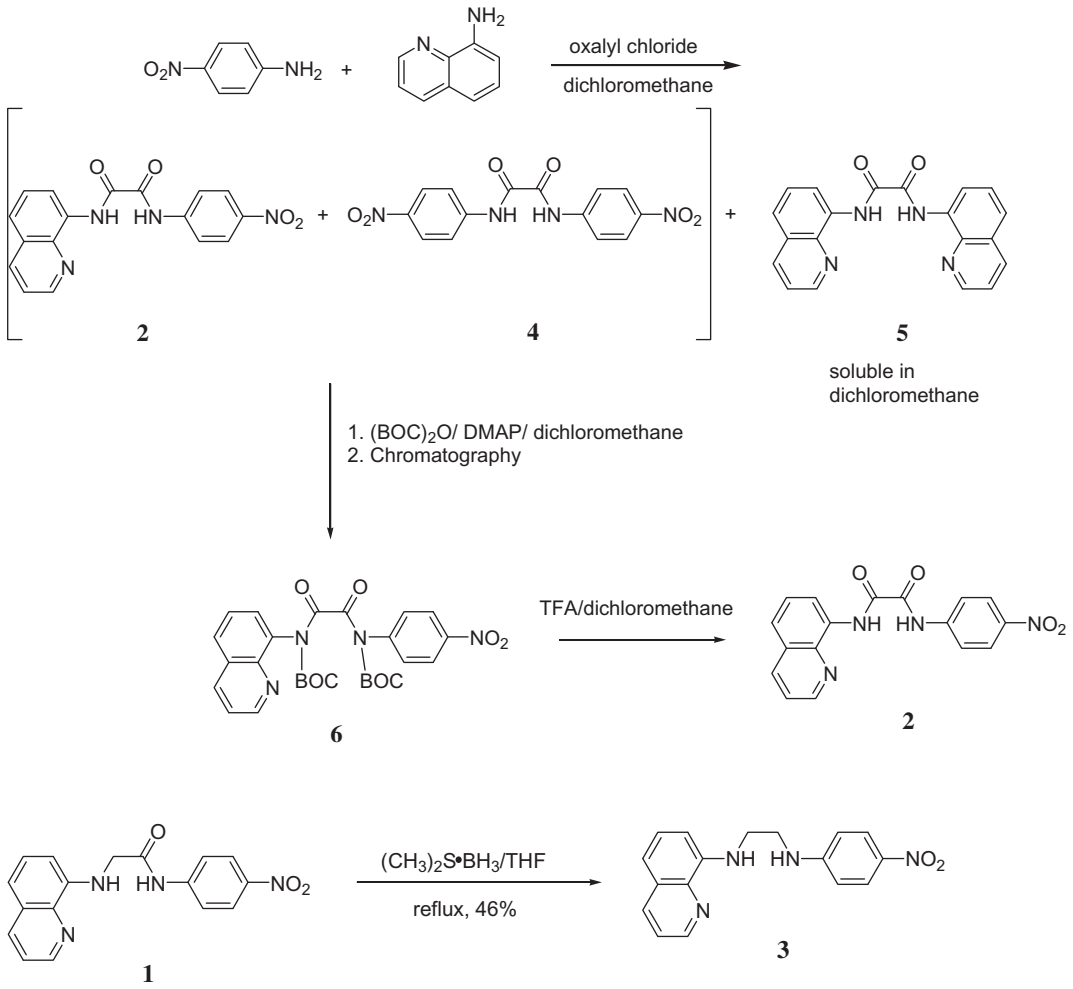
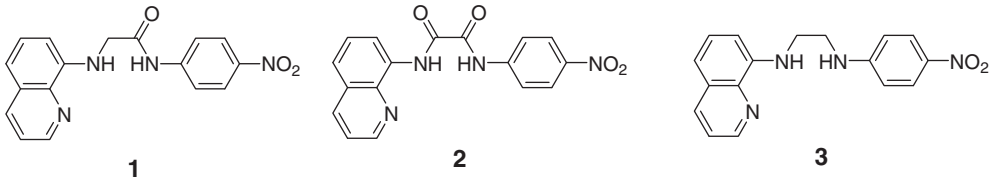


Scheme 1. The synthetic procedure for the anion receptor **2** and **3**.

and **2** with tetrabutylammonium fluoride in DMSO. As fluoride ions were added to the 20 μM solutions of **1** and **2**, λ_{max} of **1** moved from 333 to 440 nm and λ_{max} of **2** moved from 334 to 430 nm, respectively. In addition, both spectra showed clear isosbestic points at 375 and 367 nm, respectively. In the case of **3**, at the same solution and concentration, the intensity of the peak at 399 nm was decreased as fluoride ions were added and the spectra showed an isosbestic point at 420 nm (Fig. 1c). The presence of the sharp isosbestic point for these compounds indicates that only two species were present at equilibrium over the course of the titration experiment. From the titration experiments with fluoride, it was found that both compounds **1** and **2** showed drastic spectral changes and development of new intense peaks, which indicates the occurrence of N–H deprotonation while the compound **3** binds to the fluoride only through hydrogen bonds.[11] The deprotonation of the compounds **1** and **2** were confirmed through the titration experiments with tetrabutylammonium hydroxide ion.[12] Assuming 1:1 stoichiometry, a Benesi–Hildebrand plot[13] by use of absorption intensity change at 440 and 430 nm gave deprotonation equilibrium constants for the receptors **1** and **2**. In the case of the receptor **3**, absorption intensity change at 399 nm was used for the calculation of hydrogen bonded association constant. From the experiments, the deprotonation equilibrium constants of the receptors **1** and **2** for fluoride were calculated as $5.5 \times 10^2\ M^{-1}$ and $2.9 \times 10^3\ M^{-1}$, respectively, and association constant of the receptor **3** for fluoride was calculated as $1.3 \times 10^3\ M^{-1}$.

This phenomenon could be confirmed by a ^1H NMR titration. For example, In DMSO-d_6, one of the amide N–H hydrogen peaks



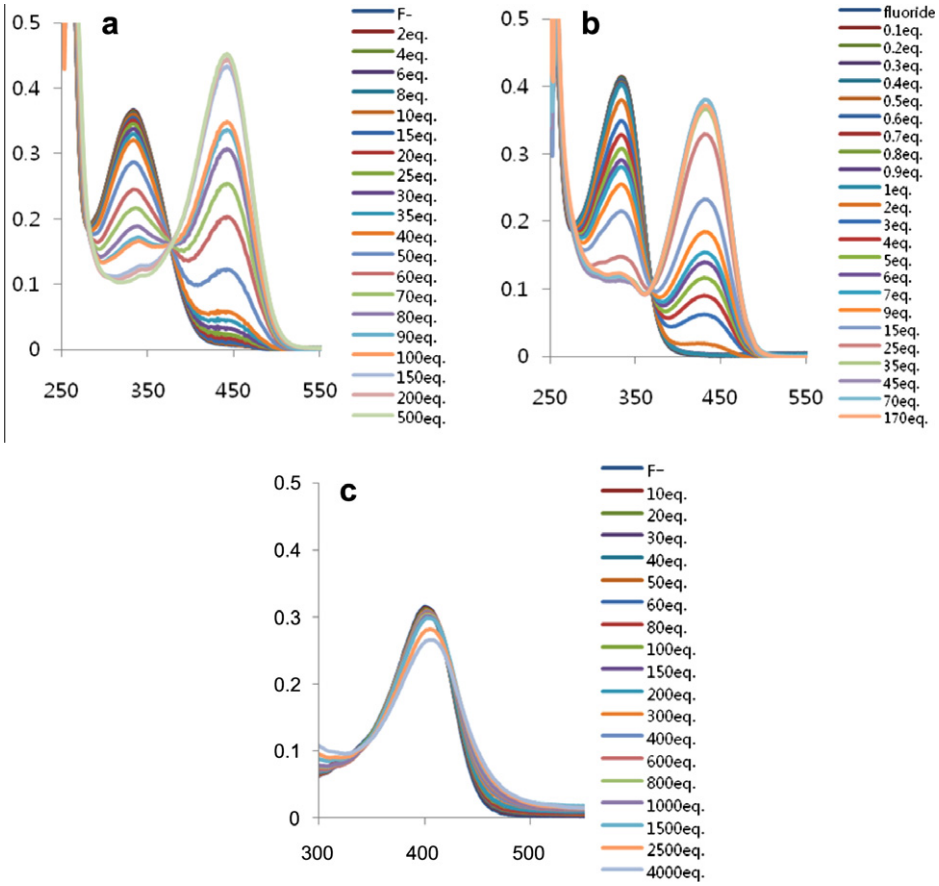


Figure 1. Family of spectra recorded over the course of titration of 20 μM DMSO solutions of the receptors **1**(a), **2**(b) and **3**(c) with the standard solution tetrabutylammonium fluoride.

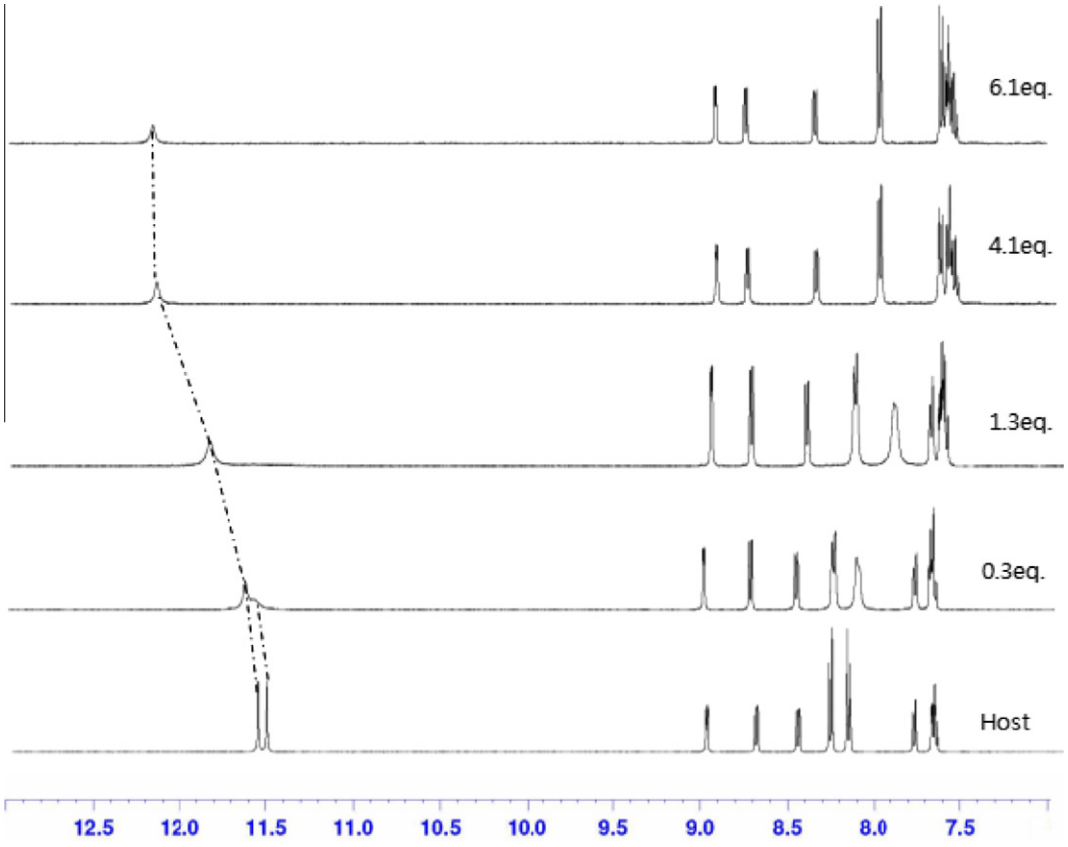


Figure 2. ^{1}H NMR spectra of 2 mM of **2** with increased amounts of tetrabutylammonium fluoride (0–4 equiv) in DMSO-d_6.

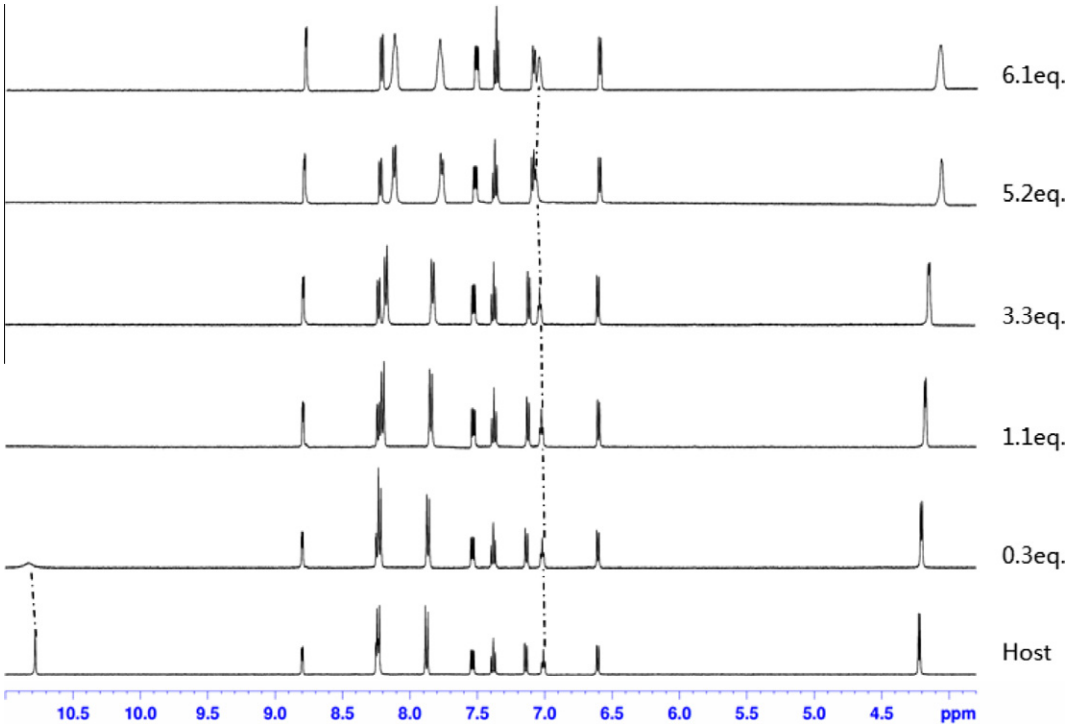


Figure 3. ^{1}H NMR spectra of 2 mM of **1** with increased amounts of tetrabutylammonium fluoride (0–5 equiv) in DMSO-d_6.

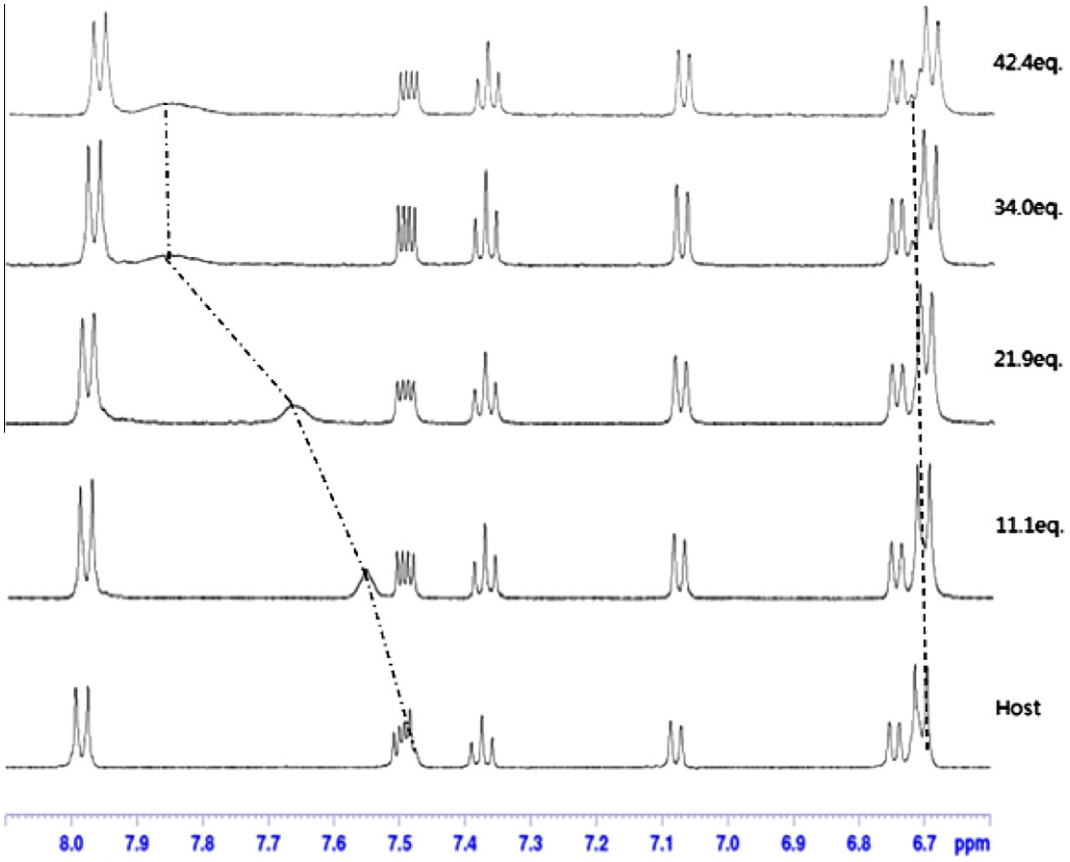


Figure 4. ^{1}H NMR spectra of 2 mM of **3** with increased amounts of tetrabutylammonium fluoride (0–34 equiv) in DMSO-d_6.

of receptor **2** became invisible upon addition of fluoride ion, which indicated deprotonation of amide hydrogen. For example, two amide peaks appeared at 11.59 and 11.54 ppm. One of amide peaks disappeared completely with 1 equiv of fluoride ion (Fig. 2). In the

Table 1
The association constants and the deprotonation equilibrium constants of the receptors **1**, **2**, and **3** with various anions in DMSO

Anion	1		2		3	
	UV	NMR	UV	NMR	UV	NMR
F^-	$^{\dagger}5.5 \times 10^2$	$^{\dagger}6.4 \times 10^2$	$^{\dagger}2.9 \times 10^3$	$^{\dagger}4.3 \times 10^3$	1.3×10^3	1.8×10^3
$CH_3CO_2^-$	4.2×10^2	3.8×10^2	$^{\dagger}4.7 \times 10^3$	$^{\dagger}3.5 \times 10^3$	2.8×10^2	1.1×10^2
$C_6H_5CO_2^-$	1.8×10^2		$^{\dagger}1.9 \times 10^2$		1.1×10	
$H_2PO_4^-$	4.1×10^2		$^{\dagger}2.1 \times 10^2$		1.2×10	

Deprotonation equilibrium constants are designated as †.

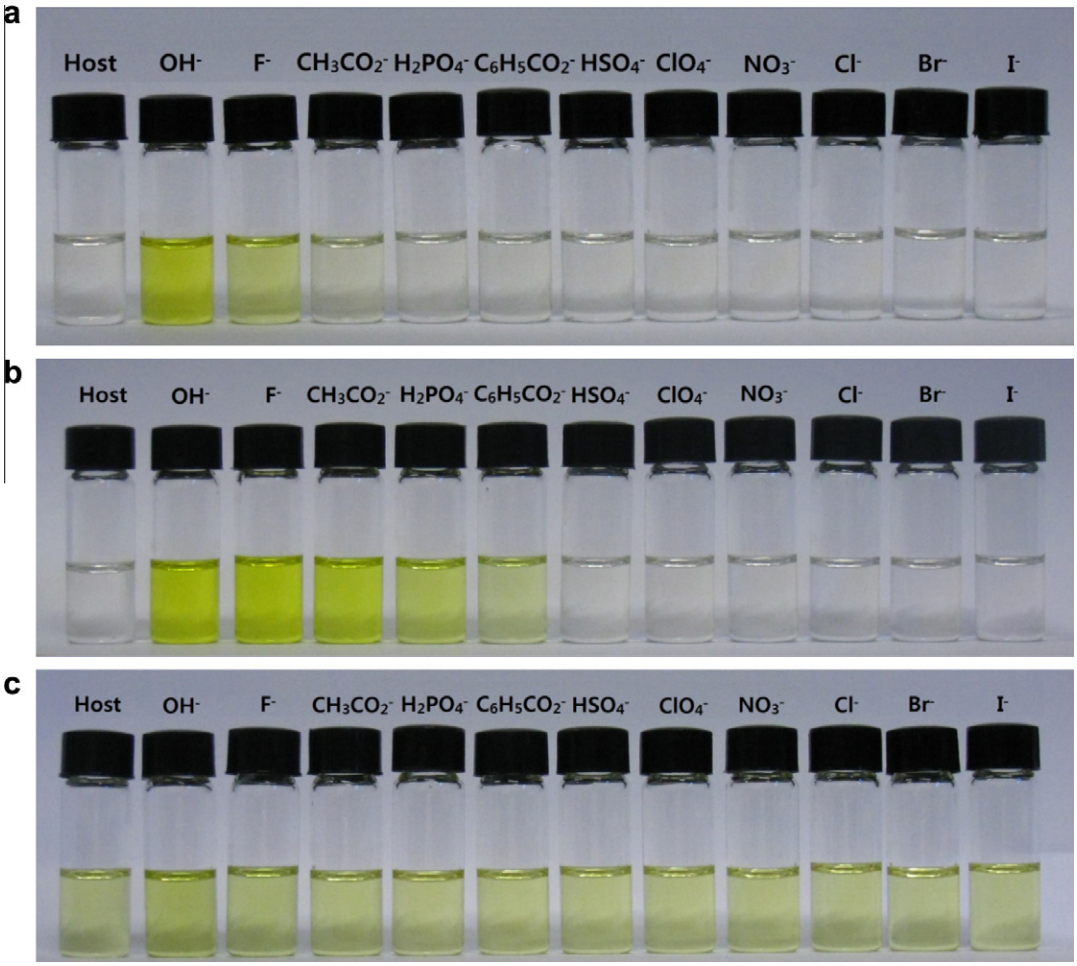


Figure 5. The color changes of the receptors **1**, **2**, and **3** when 100 μM DMSO solutions of receptors were treated with 4 equiv of various anions.

case of the receptor **1**, only the amide peak appearing at 10.78 ppm was deprotonated with 1 equiv of fluoride ion while the amine peak appearing at 7.01 ppm moved downfield slightly (Fig. 3). However, amine peaks of the receptor **3** showed only downfield shifts without deprotonation. The amine peaks of compound **3** appearing about 7.49 and 6.70 ppm showed a downfield shift until 7.85 and 6.73 ppm (Fig. 4). These results suggest that these compounds interact with fluoride through hydrogen bonds and deprotonation. For titration, one of aromatic peaks was used for the receptors **1**, **2**, and **3**. In the case of receptors **1** and **2** the peak appearing at 8.80 and 9.02 ppm was used to calculate the equilibrium constant. These peaks moved to 8.78 and 8.96 ppm, respectively and no more shifts were observed. In the case of receptor **3**, the peak appearing at 8.73 ppm was used and this peak moved until 8.70 ppm. Although the peak shifts were small, analysis of chemical shift utilizing EQNMR[14] gave equilibrium constants $6.4 \times 10^2\ M^{-1}$, $4.3 \times 10^3\ M^{-1}$ and $1.8 \times 10^3\ M^{-1}$ for the receptors **1**, **2** and **3**, respectively, which are similar values obtained from UV–vis titration.

We also investigated association constants of other anions. The results are summarized in Table 1. The receptors **1**, **2**, and **3** interact with fluoride, acetate, benzoate, and dihydrogen phosphate in DMSO. They did not bind chloride, bromide, iodide, hydrogen sulfate, perchlorate, and nitrate at all in the same solution. From the experiments, the receptor **1** was deprotonated by only fluoride and bound other anions only through hydrogen bonds. Therefore, selective detection of the fluoride ion with naked eye was possible. Figure 5 shows the color changes of the solutions of the receptor **1** upon additions of various anions in DMSO. It can be seen that the color of solution of the receptor **1** changes from colorless to yellow only in the presence of the fluoride ion. However, receptor **2** was deprotonated by all the anions it was interacting with. The most basic fluoride ion and less basic acetate ion have similar deprotonation equilibrium constants for receptor **2**. Even benzoate and

dihydrogenphosphate, which have low basicity, could deprotonate receptor **2**. High acidity of receptor **2** makes it impossible to distinguish the anions it is interacting with just through naked eye (Fig. 4b). In the case of receptor **3**, it was interacting with the anion only through hydrogen bonds. Therefore, naked detection of anions was impossible with the receptor **3** (Fig. 5c).

In summary, we designed and synthesized new anion receptors **1**, **2**, and **3** which have different N–H polarity. The receptor **1**, which has medium polarity, showed the most selective color change for the fluoride ion. However, the most polar receptor **2** showed color changes for all the anions it was interacting with and the least polar receptor **3** did not induce any color change for any anions. Therefore, fine tuning of receptor polarity could be a good strategy for the designing of selective anion receptor and made it possible to develop a selective naked eye anion receptor.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.04.081.

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10. *Synthesis of compound* **6**: To a solution of 4-nitroaniline (326 mg, 2.4 mmol), 8-aminoquinoline (341 mg, 2.4 mmol), and diisopropylethylamine (0.81 mL, 4.8 mmol) in dichloromethane under nitrogen was added oxalyl chloride (0.20 ml, 2.36 mmol) dropwise and stirred for 3 h. 246 mg of **2** and **4** were precipitated as a mixture while the compound **5** was soluble in dichloromethane. After the solid was filtered, the solid mixture was treated with dibutyldicarbonate in dichloromethane (30 mL) to give BOC protected compounds of **2** and 4. Silica gel chromatography on the silica gel (initially hexane/ethyl acetate = 5:1 later hexane/ethyl acetate = 1:1) gave 134 mg of BOC protected compounds **6**. ^{1}H NMR ($CDCl_3$, 500 MHz): 8.9 (s, 1H), 8.3 (d, J = 8.5 Hz, 2H), 8.2 (d, J = 8.0 Hz, 1H), 7.9 (d, J = 8.0 Hz, 2H), 7.6 (m, 3H), 7.4 (d, J = 3.5 Hz, 1H), 1.4 (s, 9H). 1.3 (s, 9H). *Synthesis of compound* **2**: To a solution of the compound **6** (134 mg, 0.24 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (74 μL) and stirred for 6 h. Filtration of the solid and washing with acetone gave the compound **2** (78 mg) in 96% yield. ^{1}H NMR (DMSO-d_6, 500 MHz) 11.6 (s, 1H), 11.5 (s, 1H), 9.0 (dd, J = 4 Hz, 1.5 Hz, 1H), 8.7 (dd, J = 7.5 Hz, 1 Hz, 1H), 8.5 (dd, J = 8.5 Hz, 1.5 Hz, 1H), 8.3 (d, J = 9 Hz, 2H), 8.2 (d, J = 9 Hz, 2H), 7.8 (dd, J = 8.25 Hz, 1 Hz, 1H), 7.7 (m, 2H). ^{13}C NMR (DMSO-d_6, 500 MHz) 158.8, 156.8, 149.3, 143.4, 143.3, 137.9, 136.5, 132.3, 127.7, 126.6, 124.3, 123.2, 122.3, 120.6, 116.1. HR-MS (ESI): calcd for $C_{17}H_{12}N_4O_4$+H m/e 337.0938; found 337.0933. *Synthesis of compound* **3**: To a solution of the compound **1** (200 mg, 0.62 mmol) in dried THF (3 mL) under nitrogen at 0 °C was added borane dimethyl sulfide (118 μL, 1.24 mmol) and stirred for 30 min. Then the reaction mixture was refluxed for 12 h. To a reaction mixture cooled to room temperature was added distilled water (3 mL) and stirred for 30 min. Then the reaction mixture was poured to dichloromethane (15 mL) and washed with distilled water (20 mL) three times. After the dichloromethane layer was dried with $MgSO_4$, the solvent was evaporated. Recrystallization of the residue in methanol gave unreacted compound **1** (120 mg). Chromatography on the silica gel (hexane/ethyl acetate = 1:1) gave the desire compound **3** (35 mg) in 46% yield based on recovered starting material. ^{1}H NMR (DMSO-d_6, 500 MHz) 8.7 (dd, J = 4 Hz, 1.5 Hz, 1H), 8.2 (dd, J = 8.5 Hz, 1.5 Hz, 1H), 8.0(d, J = 9.5 Hz, 2H), 7.5 (m, 2H), 7.4 (t, J = 8.0 Hz, 1H), 7.1 (d, J = 8.0 Hz, 1H), 6.8 (d, J = 7.5 Hz, 1H), 6.7 (d+m, J = 9.5 Hz, 2H+1H from amine), 3.5 (m, 4H). ^{13}C NMR (DMSO-d_6, 500 MHz) 154.6, 146.9, 144.2, 137.5, 135.9, 135.7, 128.4, 127.8, 126.2, 121.7, 113.4, 104.2, 41.5, 41.3. HR-MS (ESI): calcd for $C_{17}H_{164}N_4O_2$+H m/e 309.1352; found, 309.1345.
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