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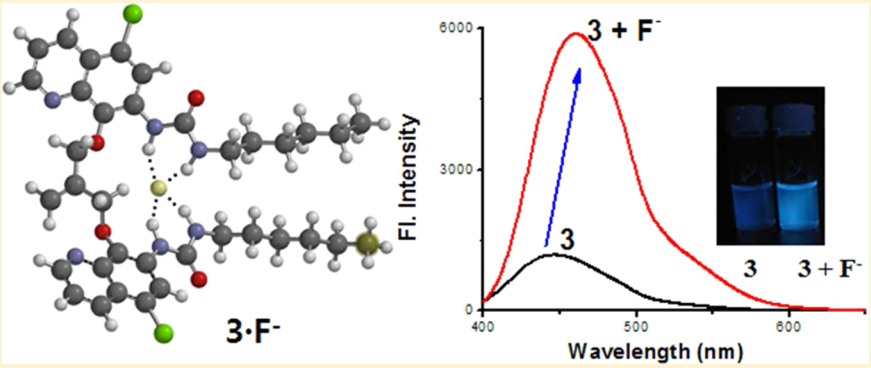
Bis-ureidoquinoline as a Selective Fluoride Anion Sensor through Hydrogen-Bond Interactions

Yunhee Jo, Nagesh Chidalla, and Dong-Gyu Cho*

Department of Chemistry, Inha University, 253 Yonghyundong, Namgu, Incheon 402-751, Republic of Korea

Supporting Information



ABSTRACT: Bis-ureidoquinoline shows a characteristic UV−vis absorbance and turn-on fluorescence changes in the presence of the fluoride anion. Such selective changes probably originate from the hydrogen-bond interactions, as shown by the ^{1}H NMR titration and DFT calculations. Bis-ureidoquinoline can be used as a fluoride-selective sensor for the detection of fluoride anions under illumination from a laboratory hand-held UV lamp.

In recent years, considerable efforts have been made to develop new receptors that are capable of sensing both neutral and charged species. In particular, colorimetric or fluorescent sensors have attracted a great deal of interest because these sensors can not only detect target species but also provide qualitative and quantitative analyses without the help of any spectroscopic instrumentation.[1] Among the anions, fluoride ions are ubiquitous in daily life and are broadly used as additives in toothpastes and water to prevent dental caries and enamel demineralization resulting from wearing orthodontic appliances.[2] Thus, fluoride ions are attractive targets for detection.[3] So far, fluoride sensors can be broadly classified into three different categories, depending on the nature of interactions between fluoride anions and sensors: (1) hydrogen-bond interactions,[4] (2) Lewis acid−base interactions,[5] and (3) fluoride anion-induced chemical reactions, including a large body of deprotonation reactions.[6] Among the hydrogen-bond-based anion sensors, ureido-based sensors have been developed by introducing their ureido group to new fluorophores.[7] In spite of the progress made in this direction, these hydrogen-bond-based sensors generally show very poor selectivity over other anions. In certain cases, it is not clear whether fluoride anions act as hydrogen-bond acceptors or weak bases in the interactions between receptors and anions. In either case, signaling groups are one of the major factors that control the characteristics of these sensors. Generally, turn-on fluorescent sensors are desired because of their large signal-to-noise ratio and superior sensitivity. Herein, we report the synthesis of a bis-ureidoquinoline sensor and its anion-binding properties. To the best of our knowledge, 7-ureido-5-chloro-quinoline derivatives have not been used as anion-binding scaffolds. Bis-ureidoquinoline obtained from 7-urido-5-chloro-quinoline not only shows fluoride selectivity over other sensors but also relies on hydrogen-bond interactions between the fluoride anion and ureido groups with the fluorescence turn-on mechanism. In particular, excellent fluoride selectivity over other anions was not commonly seen for hydrogen-bond-based chemical sensors.

To obtain a turn-on-type fluorescent sensor, we designed bis-ureidoquinoline compounds that contain two ureidoquinoline motifs linked by flexible allylic ether groups. Two ureido groups and quinolone chromophores were designed as binding motifs for the anion and reporting groups, respectively. It is expected that the F·bis-ureidoquinoline complex could reduce rotation and vibration energy, increasing the overall fluorescence intensity. The synthesis of bis-ureidoquinoline is outlined in Scheme 1. In order to obtain monoureidoquinoline **2**, reacting 7-amino-5-chloroquinolin-8-ol[8] with 1 equiv of hexyl isocyanate was first attempted. However, this reaction afforded inseparable mixtures. To overcome the problem, excess hexyl isocyanate was used; the reaction then afforded compound **1** in 78% yield after recrystallization. The carbamate group of **1** was successfully hydrolyzed in 70% yield. The target bis-ureidoquinoline (**3**) was obtained in 52% yield by reacting **2** with 3-chloro-2-chloromethyl-1-propene. The structure of bis-

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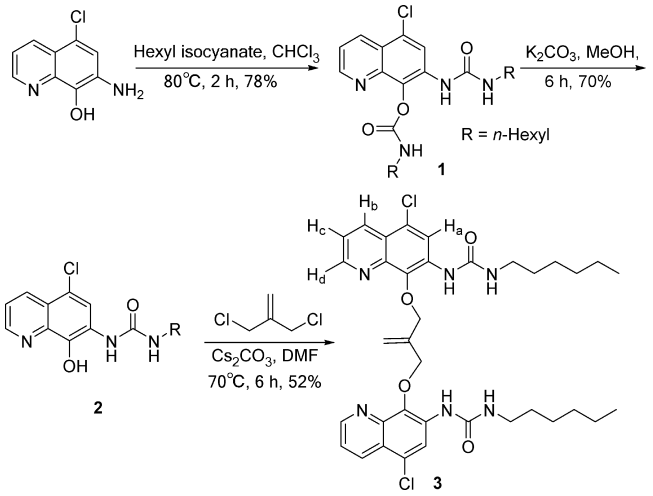
Scheme 1. Synthesis of Bis-ureidoquinoline (3)



ureidoquinoline (**3**) was confirmed using standard spectroscopic techniques. However, all our efforts to obtain a suitable single crystal of **3** and its anion complexes for X-ray diffraction analysis were unsuccessful.

To evaluate the anion-binding properties of bis-ureidoquinoline **3**, it was titrated with various anions as their tetrabutylammonium (TBA) salts. In the absence of the anions, bis-ureidoquinoline shows UV absorption bands at 256, 298, and 349 nm in CH_3CN containing 0.2% water. The absorbance of bis-ureidoquinoline ([H] = 1.0×10^{-5} M in CH_3CN) was slightly red-shifted over the entire range of wavelengths upon the addition of 20 equiv of fluoride anions ($\Delta\lambda_{261}$ = 4.5 nm and $\Delta\lambda_{349}$ = 8 nm), as depicted in Figure 1. In the case of benzoate

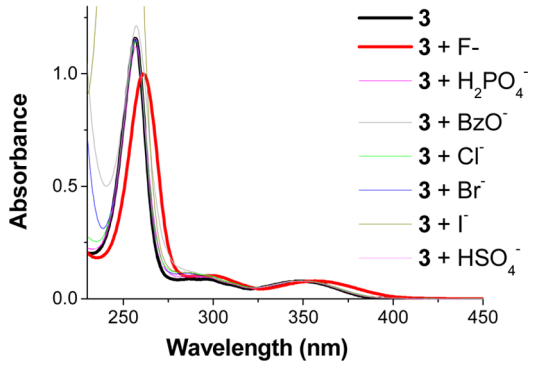


Figure 1. UV–vis spectra of **3** (1.0×10^{-5} M in CH_3CN containing 0.2% water) were recorded with or without 20 equiv of various anions as a TBA salt.

anions, the UV–vis spectrum of **3** was very slightly red-shifted, with an accompanying slight increase in the absorbance. There was no noticeable change in the UV–vis spectrum of **3** in the presence of other anions. We monitored the effects of water in CH_3CN on the spectral behavior of bis-ureidoquinoline. As the water content was increased up to 0.5% in CH_3CN, the absorbance of bis-ureidoquinoline was very slightly red-shifted in the presence of the TBA fluoride salt (TBA·F). However, the degree of the red-shift was attenuated as the water content in CH_3CN increased (Figure S1 in the Supporting Information). Therefore, all further titrations were conducted in CH_3CN containing 0.2% water. During the fluoride titration, several isosbestic points were observed. These isosbestic points are considered as an indirect evidence of the 1:1 binding stoichiometry of bis-ureidoquinoline and the fluoride anion as a TBA salt. In addition, the 1:1 binding stoichiometry of bis-ureidoquinoline and TBA·F was further confirmed by Job plot analysis under the same condition and host concentration (Figure 2). The change in the absorbance of bis-ureidoquino-

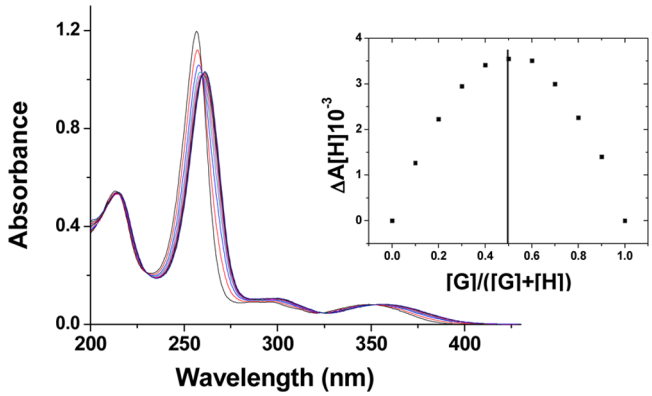


Figure 2. Evolution of the UV–vis spectrum of **3** (1.0×10^{-5} M in CH_3CN containing 0.2% water) during the titration with tetrabutylammonium fluoride (TBA·F; 0–20 equiv). Inset: Job plot for the interaction between **3** and TBA·F.

line obtained from the above-mentioned titration at 385 nm is plotted (see the Supporting Information). A nonlinear regression analysis was carried out, showing that the obtained curve is tightly fitted to the 1:1 binding equation as well. All the absorbance changes were recorded at 385 nm, unless stated otherwise. The binding constant for the fluoride anion was determined (K_a = $1.7 \times 10^4 \pm 1100$ M^{-1}) in CH_3CN containing 0.2% water, as shown in Table 1. For the benzoate

Table 1. Anion-Binding Constants (K_a; M^{-1}) of 3 (1.0×10^{-5} M) in CH_3CN Containing 0.2% Water at 25 °C[a]

	UV–vis	fluorescent
F^-	$1.7 \times 10^4 \pm 110$	$1.2 \times 10^4 \pm 2100$
Cl^-	N.D.	≪1
Br^-	N.D.	N.D.
I^-	N.D.	N.D.
BzO^-	N.D.	N.D.
HSO_4^-	N.D.	N.D.
$H_2PO_4^-$	N.D.	$8.9 \times 10^3 \pm 1100$

[a]All the anions were used in the form of their respective tetrabutylammonium salts. N.D.: No detectable binding phenomenon was observed in the UV–vis absorption or fluorescent titration.

anions, the obtained binding curve was still linear to the various concentrations of benzoate at 280 nm (see the Supporting Information). Such a fingerprint type of UV–vis spectroscopic change in the presence of the fluoride anion was surprising. Thus, all anion titrations were reexamined in pure CH_3CN. The binding constant of the fluoride anion increased to $3.4 \times 10^4 \pm 2900$ M^{-1} (Figure S1 in the Supporting Information). On the other hand, UV–vis spectroscopic changes for other anions were barely seen, even in pure CH_3CN. Such a selectivity trend and characteristic UV–vis absorption changes of **3** were similar to those of sapphyrins, fluoride selective pentapyrrolic aromatic macrocycles.[4a] Thus, fluorescent titra-

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tions were carried out to see the possibility that fluorescent changes could be enlarged for certain anions.

The fluorescent spectra of bis-ureidoquinoline **3** were recorded in the presence of 20 equiv of each anion. The fluorescence quantum yield of **3** (Φ_F = 16.5%) was determined relative to that of coumarin-120 in CH_3CN.[9] Anions F^-, $H_2PO_4^-$, and Cl^- increased the original intensity of bis-ureidoquinoline **3** (Figure 3) in CH_3CN containing 0.2% water.

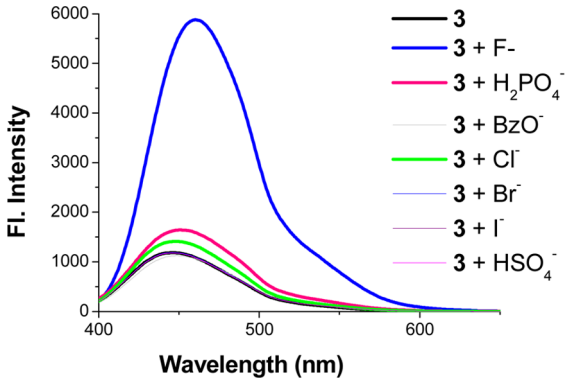

Figure 3. Fluorescent spectra of **3** (1.0×10^{-5} M in CH_3CN containing 0.2% water) with and without 20 equiv of various anions as tetrabutylammonium salt.

In particular, a 3-fold increase was observed with the fluoride anion. The binding constants for other anions were further examined by fluorescent titrations. As summarized in Table 1, **3** showed the highest anion-binding affinity to F^- anions (K_a = 1.2×10^4 M^{-1}, the Supporting Information), followed by $H_2PO_4^- \gg Cl^-$. Upon adding Cl^-, the observed fluorescent changes were directly proportional to the concentration change of chloride ($K_a \ll 1$, the Supporting Information). It should be also noted that the spectral changes of **3** (red-shifts) could be due to the expected complex between **3** and anions during the UV–vis and fluorescent titrations.

^{1}H NMR spectroscopic titration in CD_3CN containing 0.2% of D_2O was carried out to know whether the F^--induced optical changes of **3**·F^- are associated with a hydrogen bond or with simple deprotonation (Figure S4 in the Supporting Information). The NH peaks of four ureido groups and the CH peak of the quinoline ring (H_a) were shifted downfield upon the addition of increasing quantities of TBA·F (see the assigned H_a proton of **3** in Scheme 1). In contrast, all the other quinoline protons were slightly upfield shifted. These observations clearly indicated the existence of two hydrogen bonds ($F^-\cdots$NH and $H_a\cdots$O=C). In addition, a triplet peak of HF_2^- on the ^{1}H NMR spectrum has been considered as a hallmark for fluoride-induced deprotonation reaction.[6j,k] No trace of the triplet peak was seen during the titration in acetonitrile-d_3 with or without 0.2% D_2O. In addition, the participation of hydrogen bonds with **3** was further supported by ^{19}F-NMR titration.[10,11] Moreover, no biphasic behavior of fluoride anions was observed for UV–vis titrations in the presence of 20 equiv of fluoride anions. Thus, the observed spectroscopic changes of **3** in the presence of fluoride anions could originate from hydrogen-bond interactions rather than a simple deprotonation reaction. In the case of $H_2PO_4^-$ titration, the chemical shift changes of NHs were similar to those of fluoride titrations, although the chemical shift of H_a was shifted upfield (Figure S6 in the Supporting Information). Therefore, we concluded that the binding mode of **3** to $H_2PO_4^-$ anions should be different from that of fluoride anions. Considering the ineffective HSO_4^--binding properties for **3** (Table 1), $H_2PO_4^-$ anions can build more complex hydrogen-bond networks with **3** due to the hydrogen-bond donor and acceptor properties of the $H_2PO_4^-$ anions.[12]

To understand in detail the binding mode of **3**·F^-, we conducted theoretical calculations based on DFT methods at the EDF2/6-31G* level of theory. In the optimized structure, the F^- anion is accommodated in the cavities of **3** (Figure S7 in the Supporting Information). In the optimized structures of **3** with other halide anions, the hydrogen-bond length (or the cavity size) increased as the larger anions were present in the cavity of **3**. Consequently, other anions cannot be fitted in the cavity of **3**. It should be also noted that bis-ureidoquinoline is highly electron-rich and the length of the F···HN hydrogen bond attached to quinoline is slightly longer than others. Thus, the pK_a values of the NHs attached to quinoline is expected to be higher than that of other uriedo sensors. These conditions favor the hydrogen-bond interactions rather than deprotonation reactions.

Bis-ureidoquinoline **3** showed a fingerprint-type change in its UV–vis spectra in the presence of fluoride anions compared to other anions (Figure 1). It is also true that a poor fluoride selectivity was only seen in the case of $H_2PO_4^-$ anions ($K_a(F^-)/K_a(H_2PO_4^-)$ = 1.4) (Table 1). Nonetheless, it has characteristic fluoride selectivity with its own merits including the turn-on fluorescent signal and relatively simple synthesis as compared with a few known hydrogen-bond-based sensors.[4] Further competition experiments were also carried out by adding 20 equiv of F^- to the solutions of compound **3** in the presence of 20 equiv of other anions, as shown in Figure 4.

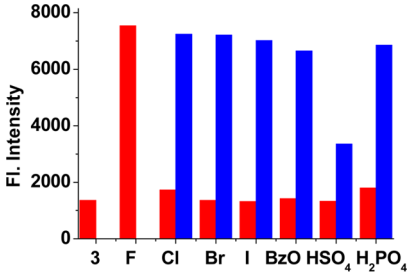

Figure 4. Anion selectivity of **3** (1.0×10^{-5} M in CH_3CN containing 0.2% water). The red bars represent the emission intensity of **3** in the presence of anions (20 equiv). The blue bars represent the emission intensity that occurs upon the subsequent addition of 20 equiv of F^- to the above solution.

None of the tested anions interfered with the detection of fluoride anions except HSO_4^-, although the fluorescent intensity of the solution containing both HSO_4^- and F^- anions was still high. This result clearly indicates that bis-ureidoquinoline is barely affected by these coexisting anions. It also strongly suggests that bis-ureidoquinoline **3** could be used as a chemosensor under illumination from a laboratory hand-held UV lamp. As shown in Figure 5, the presence of fluoride was easily detected by observing the increased fluorescent intensity of **3**.[13]

In summary, the synthesis and anion-binding properties of a bis-ureidoquinoline sensor were reported. The bis-ureidoquinoline sensor was obtained by dimerizing 7-urido-5-chloroquinoline[14] as a new anion-binding scaffold with an ether

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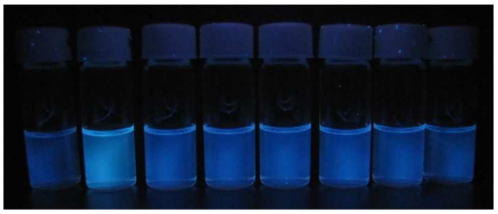

Figure 5. Changes in fluorescence observed upon the addition of various anions (20 equiv) to the solution of **3** (5.0×10^{-6} M in CH_3CN containing 0.2% water) under a laboratory hand-held UV lamp. From left to right: no anion, F^-, Cl^-, Br^-, I^-, BzO^-, HSO_4^-, $H_2PO_4^-$. All the salts used were in the form of tetrabutylammonium salt.

linkage. The obtained bis-ureidoquinoline sensor has a characteristic UV−vis absorbance and shows turn-on fluorescence changes in the presence of a fluoride anion. Moreover, the turn-on fluorescent signals were not interfered with by the presence of other anions. Such selective changes for fluoride anions could be attributed to the hydrogen-bond interactions between two uriedo groups and fluoride anions. This claim was supported by the ^{1}H NMR titration and DFT calculations. In addition, the bis-ureidoquinoline sensor can be used for the detection of fluoride anions under illumination from a laboratory hand-held UV lamp.

EXPERIMENTAL SECTION

General and Synthetic Experiments. Reagents with the highest commercial quality were purchased and used without further purification, unless otherwise stated. Yields of the synthesized compounds were measured after chromatographic purification.

5-Chloro-7-(3-hexylureido)quinolin-8-yl Hexylcarbamate (1). 7-Amino-5-chloroquinolin-8-ol (0.20 g, 1.03 mmol) and hexyl isocyanate (0.75 mL, 5.14 mmol) were dissolved in anhydrous $CHCl_3$ (0.7 mL). The resulting solution was heated at 80 °C for 2 h under N_2. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. After the obtained residue was thoroughly washed with hexane, the desired compound **1** was obtained in 78% yield as a yellow solid (0.36 g, 0.80 mol); mp: 178−181 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83 (m, 2H), 8.42 (m, 2H), 7,96 (m, 1H), 7.53 (d, J = 8.6, 4.3 Hz, 1H), 7.10 (m, 1H), 3.11 (m, 4H), 1.48 (m, 3H), 1.30 (m, 13H), 0.88 (m, 6H);^{13}C NMR (100 MHz, DMSO-d_6) δ 154.7, 154.0, 150.9, 142.0, 134.0, 132.1, 126.1, 120.8, 120.5, 119.7, 40.8, 31.1, 31.0, 29.5, 29.3, 26.2, 25.9, 22.2, 22.1, 13.9, 13.9; HRMS−FAB: m/z $[M + H]^+$ calcd for $C_{23}H_{34}ClN_4O_3$: 449.2319; found:449.2316.

1-(5-Chloro-8-hydroxyquinolin-7-yl)-3-hexylurea (2). K_2CO_3 (0.23 g, 1.67 mmol) was added to the solution of **1** (0.25 g, 0.56 mmol) in MeOH (8 mL). The mixture was stirred at room temperature for 6 h. Then, the mixture was filtered through a Celite pad, and MeOH was evaporated under reduced pressure. The obtained residue was diluted with ethyl acetate and neutralized with a saturated aqueous solution of citric acid. The organic portions were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The obtained solid was then washed with diethyl ether and filtered off. After drying, the desired compound **2** was obtained in 70% yield as an off-white solid (0.38 g, 1.19 mmol); mp 190−192 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.35 (bs, 1H), 8.88 (d, J = 4.2 Hz, 1H), 8.72 (s, 1H), 8.38 (m, 2H, NH and CH), 7.53 (dd, J = 8.5, 4.2 Hz, 1H), 7.04 (t, J = 5.7 Hz, 1H), 3.10 (dt, J = 6.4, 6.4 Hz, 2H), 1.43 (m, 2H), 1.28 (m, 6H), 0.87 (t, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.1, 149.1, 138.3, 138.0, 132.4, 126.5, 120.4, 120.3, 119.7, 118.4, 31.0, 29.5, 26.0, 22.1, 13.9; HRMS−EI: m/z $[M]^+$ calcd for $C_{16}H_{20}ClN_3O_2$: 321.1244; found:321.1241.

1,1′-(((2-Methylenepropane-1,3-diyl)bis(oxy))bis(5-chloroquinoline-8,7-diyl))bis(3-hexylurea) (3). Cs_2CO_3 (0.46 mg, 1.40 mmol) was added to a solution of **2** (0.09 g, 0.28 mmol) and 3-chloro-2-chloromethyl-1-propene (15 μL, 0.14 mmol) in anhydrous DMF (3 mL). The resulting mixture was heated at 70 °C for 6 h under N_2. After cooling to room temperature, the organic solvent was removed under reduced pressure. The residue was diluted with EtOAc and washed with water. Then, the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified over silica gel to afford **3** as a yellowish solid (0.174 g, 92%); mp 59−60 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 2H), 8.90 (bs, 2H), 8.87 (dd, J = 4.2, 1.9 Hz, 2H), 8.48 (d, J = 8.5 Hz, 2H), 7.41 (dd, J = 8.5, 4.3 Hz, 2H), 6.02 (d, J = 5.9 Hz, 2H), 5.38 (s, 2H), 5.01 (s, 2H), 3.19 (dt, J = 6.6, 6.6 Hz, 4H), 1.37 (m, 4H), 1.14 (s, 12H), 0.79 (t, J = 3.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 151.1, 142.9, 138.6, 138.1, 135.0, 133.7, 128.4, 124.4, 122.5, 120.5, 120.2, 80.2, 40.3, 31.7, 30.2, 26.7, 22.7, 14.2; HRMS−FAB: m/z $[M + H]^+$ calcd for $C_{36}H_{45}Cl_2N_6O_4$: 695.2879; found:695.2875.

ASSOCIATED CONTENT

Supporting Information

Contains experimental, spectroscopic titrations, DFT calculations, and spectral data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*Fax: +82 32 867 5604. E-mail: dgcho@inha.ac.kr (D.-G.C.).

Notes

The authors declare no competing financial interest.

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(11) In the absence of **3**, the signal of F^- was shifted upfield while the chemical shift of HF_2^- was not changed as the concentration of F^- increased. During the ^{19}F-NMR titration in DMSO-d_6, the chemical shift of F^- shown at −101.8 ppm disappeared and a small broad peak vaguely showed up at −92.5 ppm. Typically, upon the addition of 1 equiv of F^-, both of HF_2^- and F^- signals completely disappeared (Figure S5 in the Supporting Information). In addition, it was reported that the chemical shift of HF_2^- (^{19}F-NMR) is shown due to the small amount of water in DMSO-d_6. The concentration of F^- and water also affects the chemical shift of F^- without a host molecule. See: Goursaud, M.; De Bernardin, P.; Dalla Cort, A.; Bartik, K.; Bruylants, G. *Eur. J. Org. Chem.* **2012**, *2012*, 3570.

(12) (a) Sessler, J. L.; Cho, D. G.; Lynch, V. *J. Am. Chem. Soc.* **2006**, *128*, 16518. (b) Hossain, M. A.; Işiklan, M.; Pramanik, A.; Saeed, M. A.; Fronczek, F. R. *Cryst. Growth Des.* **2012**, *12*, 567. (c) Zhang, Y.; Zhang, R.; Zhao, Y.; Ji, L.; Jia, C.; Wu, B. *New J. Chem.* **2013**, *37*, 2266.

(13) Detection of fluoride anions in toothpaste was tried. However, the extracted aqueous solution from the toothpaste was precipitated in a solution of **3** (1.0×10^{-5} M in CH_3CN containing 0.2% water). In the condition that requires more water, bis-ureidoquinoline lost its hydrogen-bonding ability for fluoride anions (Figure S8 in the Supporting Information). The extracted aqueous solution was prepared according to the reported procedure. See: Marquez, M.; Anzenbacher, P. *J. Am. Chem. Soc.* **2007**, *129*, 7538.

(14) Upon the addition of F^- anions, biphasic behaviors (deprotonation and binding) of **2** were clearly seen due to the acidic phenolic OH group. The binding properties of **3** are quite different from those of **2**. Thus, the binding properties of **2** will be independently discussed elsewhere.