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Anion Sensing Properties of New Colorimetric Chemosensors Based on Thiourea and Urea Moieties

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A new colorimetric sensors containing thiourea (1-(4-nitrophenyl)-3-quinolin-6-ylthiourea; **1**) and urea(1-(4-nitrophenyl)-3-quinolin-6-ylurea; **2**) moieties for fluoride were designed and synthesized. These simple receptors were characterized their stoichiometry, and investigates the mechanism of their selectivity as anion receptors. The addition of tetrabutylammonium fluoride salts to the solution of receptors caused a dramatically and clearly observable color changes from colorless to yellow. To examine their application as anion receptors by UV-vis and ^{1}H NMR spectroscopy results revealed their higher selectivity for fluoride ion than other anions. The receptors and fluoride ion formed a 1:1 stoichiometry complex through strong hydrogen bonding interactions in the first step, followed by a process of deprotonation in presence of an excess of F^- in DMSO solvent.

Key Words : Fluoride sensor, Urea, Thiourea, Colorimetric sensor, Naked-eye

Introduction

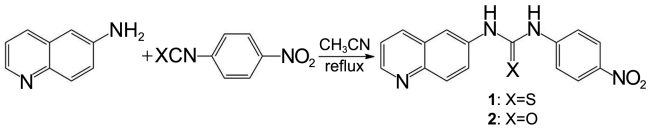
The recognition and sensing of artificial receptors has been an important area of current research that has added to the understanding of host-guest interactions occurring in chemical and biological systems.[1] Recently, interest has increased in the synthesis of artificial receptors capable of sensing specific anionic guests.[2,3] This is due to the important roles played by anions in biology, medicine, catalysis, and the environment. In particular, anionic receptors have the ability to selectively recognized and sense anionic analysts through visible, electrochemical, and optical responses.[4,5] Moreover, the development of artificial anion receptors capable of recognizing biologically relevant anions such as fluoride, chloride, phosphate, and acetate anion has attracted considerable interest.[6] Among those common anions, fluoride ion received the most attention from chemists because of its unique properties.[7-10]

As we all know, a small quantity of fluoride ion can prevent dental caries and excessive of fluoride ion can lead to human fluorosis. In addition, as the smallest and the most electronegative atom, fluoride can form the strongest hydrogen-bond interaction with hydrogen-bond donors.[11,12] However, the recognition of fluoride ion over oxygen-containing anion especially the acetate or benzoate or dihydrogen phosphate ion is still difficult due to their similar basicity and surface charge density.

Most artificial anion receptors contain NH fragments that act as hydrogen bond donors for the binding of anions such as receptors based on pyrroles, amides, ureas, thioureas, or sulfonamides.[13-20] In particular, the urea and thiourea groups have been used to construct a considerable number of receptors for anionic species. These groups have particularly high affinities for oxo-anions, as they are capable of forming two hydrogen bonds to the oxo-anion.[11,13-15,21] Therefore, many artificial anion receptors containing the urea/thiourea subunits have been designed, synthesized and tested for anion recognition and sensing during the past few decades. Many examples are available on the selective phenylurea and phenylthiourea moieties receptor molecules for the fluoride ion. For example, Jose *et al*.[5] reported novel colorimetric receptors for selective fluoride ion sensing by introducing urea/thiourea subunits (phenylurea and phenylthiourea) into an anthraquinone spacer acting as a chromogenic signaling subunit. In addition, Shao *et al*.[22] investigated a simple colorimetric anion receptor (*β-N*-(*p*-nitroaniline)-phenylthiourea) containing NH binding sites. However, few reports have described the change in color in the visible region of the spectrum, which would offer naked eye sensing of the fluoride ion. These color changes, as signaling an event detected are widely used owing to the low cost or lack of equipment required.

With this information, we designed and synthesized two new receptors (Scheme 1) containing urea and thiourea moieties. Both **1** and **2** contain strong electron withdrawing substituent (nitro group) at positions to the benzene ring. We expect that a more increased hydrogen bonding donor ability of the urea and thiourea moieties for efficient anions binding.

The anion binding properties of the two receptors were



Scheme 1. Syntheses of receptors **1** and **2**.

investigated by UV-vis spectroscopy, ^{1}H NMR titration experiments and theoretical investigations. Experimental and theoretical results demonstrated the receptors high sensitivity and selectivity to only F^- among Cl^-, Br^-, I^-, HSO_4^-, $H_2SO_4^-$, $H_2PO_4^-$, NO_3^-, SCN^-, ClO_4^-, salicylate, acetate, and benzoate ions, thereby supporting their use as a convenient detector for the fluoride ion.

Experimental

Reagents and Apparatus. All the anions were added in the form of tetrabutylammonium (TBA) salts, which were purchased from Sigma-Aldrich Chemical, stored in a vacuum desiccator containing self-indicating silica and dried fully before using. DMSO was dried with CaH_2 and then distilled in reduced pressure. All other chemicals used are commercially available reagents of analytical grade without further purification. All experiments were carried out at room temperature. Water-sensitive reactions were performed under argon. IR spectra were recorded on a Perkin-Elmer 1750 FT-IR. The ^{1}H NMR spectra were recorded with Bruker Advance 300 spectrometers. Chemical shifts are reported in parts per million (ppm) downfield from TMS. UV-vis spectra were run at 25 ºC on an HP 8453 system. Low- and high-resolution fast atom bombardment-mass spectrometry was measured using a JEOL JMS-700 (MStation) instrument.

General Procedure for the Synthesis of Receptors 1 and 2. Receptor **1** (1-(4-nitrophenyl)-3-quinolin-6-ylthiourea) was synthesized by the reaction 6-aminoquinoline with 1-isothiocyanato-4-nitrobenzene. To a solution of 6-aminoquinoline (18.7 mg, 1.3 mmol) in a 15 mL solution of acetonitrile was slowly added 1-isocyanato-4-nitrobenzene (24.3 mg, 1.35 mmol) in 15 mL of acetonitrile over 20 min, after which the mixture was refluxed for 4 h in a nitrogen atmosphere. The solid product was collected by filtration and washed with acetonitrile in 70% yield (27.3 mg); mp: 192 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.66 (*s*, 1H), 10.56 (*s*, 1H), 8.96 (*d*, *J* = 0.9 Hz, 1H), 8.42 (*d*, *J* = 2.4 Hz, 1H), 8.24 (*d*, *J* = 8.7 Hz, 2H), 7.99 (*t*, 2H), 7.87 (*d*, *J* = 8.7 Hz, 2H), 7.72 (*t*, 1H), 7.61 (*t*, 1H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 180.2 (*s*, C=S), 150.3, 146.6, 145.9, 143.0, 137.5, 136.2, 129.5, 128.5, 127.7, 124.9, 122.4, 122.2, 120.8 (*s*, C); ESI-MS: *m*/*z* (%): 325.00 (M^+, 100%).

Receptor **2** (1-(4-nitrophenyl)-3-quinolin-6-ylurea) was prepared by using the above procedure with 6-aminoquinoline (18.7 mg, 1.3 mmol) and 1-isocyanato-4-nitrobenzene (22 mg, 1.35 mmol) being stirred under an inert atmosphere at 90 °C for 3 h. The resulting precipitate was filtered and washed thoroughly with acetonitrile in 76% yield (32 mg); mp: 268 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.70 (*s*, 1H), 9.40 (*s*, 1H), 8.87 (*d*, *J* = 2.4 Hz, 1H), 8.55 (*d*, *J* = 2.4 Hz, 1H), 8.23 (*d*, *J* = 8.7 Hz, 2H), 7.93 (*t*, 3H), 7.76 (*d*, *J* = 9.0 Hz, 2H), 7.60 (*m*, 2H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 152.1 (*s*, C=O), 149.2, 146.1, 144.5, 141.3, 137.6, 135.5, 130.1, 128.9, 125.2, 123.6, 122.4, 118.2, 114.0 (*s*, C); ESI-MS: *m*/*z* (%): 309.08 (M^+, 100%).

Calculation Methods. The two receptors **1** and **2** with anions (F^- and AcO^-) and complexes were optimized by density functional theory calculations using the nonlocal density function of Becke's three parameters employing the Lee-Yang-Parr functional with 2-31G* basis sets using the Gaussian 98 program suite.[23] The interaction energy is simply obtained by the energy of the complex subtracted by the sum of the energies of the constituents. Generally, basis set superposition error (BSSE) correction should be included to obtain accurate interaction energy.[24] However, as the interaction in this study was very strong due to charged hydrogen bonding the BSSE was expected to be negligible compared with the magnitude of the total interaction energies.

Results and Discussion

Optical Responses of Receptors. The anion recognition properties were firstly investigated by monitoring the UV-vis spectral changes of receptors upon addition of different anions. All the UV-vis behavior of receptors was studied in DMSO solvent. Figure 1 shows the absorption spectra of receptor **1** in the presence of the 1 equiv. of anions. In the absence of anions, **1** exhibits one main band (λ_{max}) at about 346 nm in the UV-vis absorption spectrum. When receptor **1** formed a complex with F^- ions, the absorption peak at 346 nm disappeared and a new peak appeared at 417 nm, having been red-shifted by about 71 nm to a longer wavelength. However, no red-shift occurred when receptor **1** was treated with any of the other ions, except benzoate and acetate.

In Figure 2 showing the absorption spectra of receptor **2** in the presence of the anions (1 equiv.) the absorption peak at 347 nm was red-shifted to 483 nm ($\Delta\lambda_{max}$ = 136 nm) when F^- ions were added to receptor **2** in the DMSO solution. Under the same experimental conditions, acetate and benzoate only induced a tiny spectral change of receptor **2**. In addition, other anions not cause notable spectral changes of receptor **2**. In these results, the selectivity of the fluoride ion was greater than the other anions.

The presence of anions could also be detected at room temperature by the naked eyes, as shown in Figure 3. The color change of receptor **1** from colorless to yellow upon the

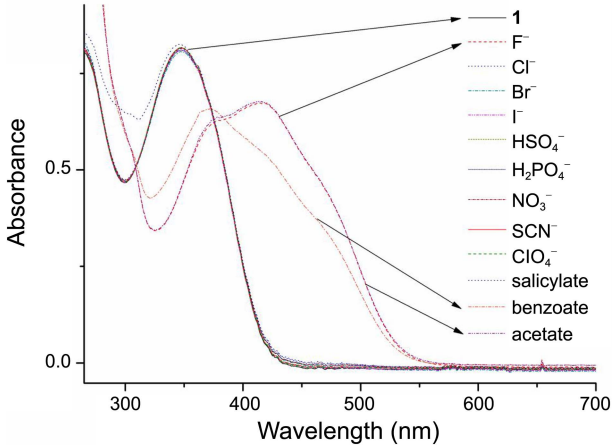


Figure 1. Absorption spectra of **1** (4×10^{-5} M) in the absence and presence of different anions (1 equiv.) in DMSO.

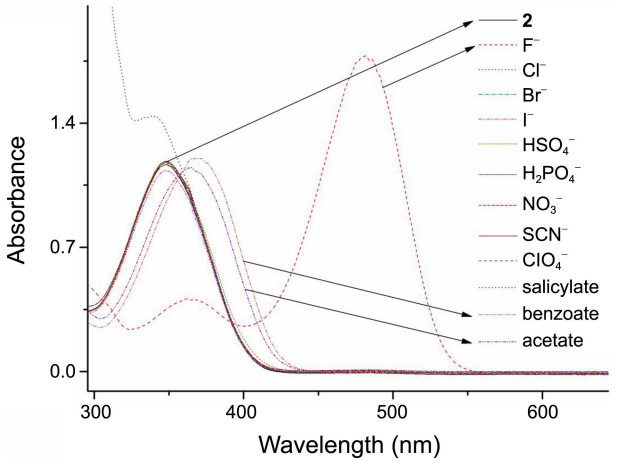


Figure 2. Absorption spectra of **2** (4×10^{-5} M) in the absence and presence of different anions (1 equiv.) in DMSO.

Figure 3. Color changes of receptors (a) **1** and (b) **2** in DMSO (4×10^{-5} M) before and after the addition of tetrabutylammonium anions (1×10^{-3} M) (Sal=salicylate, Ben=benzoate).

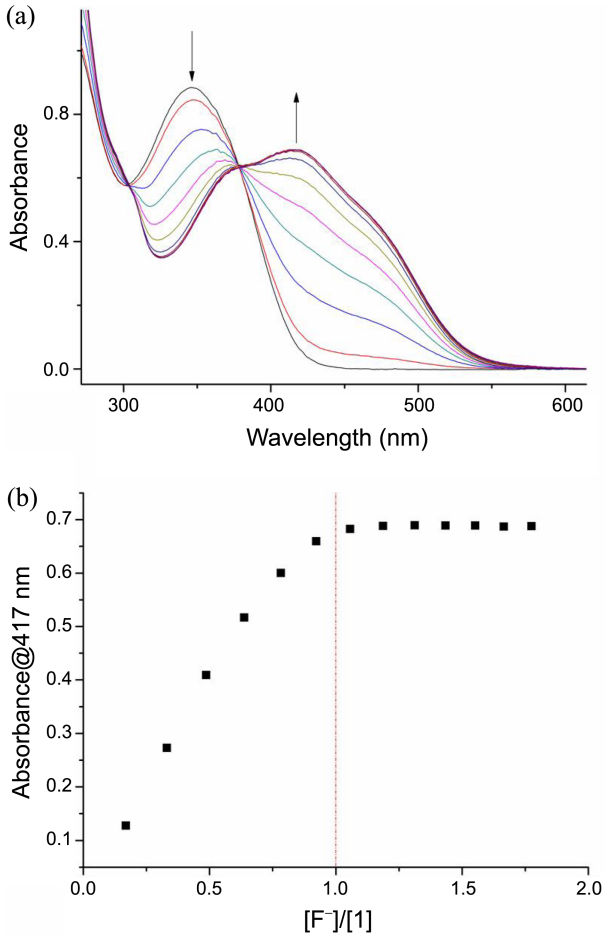
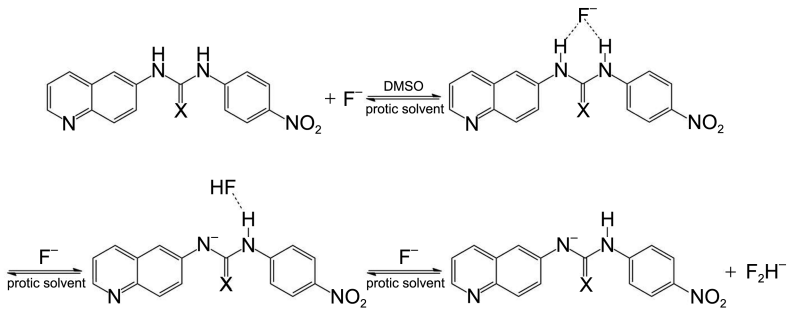


Figure 4. (a) Absorption spectra of **1** (4×10^{-5} M) after addition of TBAF in DMSO. (b) The stoichiometry analysis of fluoride complex **1**-F^- by mole fraction plot analysis.

addition of F^-, acetate, and benzoate anions was easily observed by the naked eye even at one equivalent. In contrast, almost no color change was evident upon the addition of any of the 9 ions (as shown in Fig. 3(a)). However, similar color changes were also seen upon addition of F^- to DMSO solution of receptor **2**, but in this case the color change was much weaker than that of acetate and benzoate (Fig. 3(b)). In these results, the color changes are most probably due to the formation of hydrogen bond interactions between the urea or thiourea groups and the corresponding anions.[10,12,13,17] Most importantly both receptors exhibited a high selectivity for F^- and induced a distinct color change that could be observed. Interestingly, addition of some protic solvents such as water, methanol or ethanol to the solution receptors bound to fluoride ion, the color changes were reversed indicating that the recognition process was reversible and the interactions were in essence H-binding interaction. Also, deprotonation of receptors by excessive fluoride ion in DMSO led to a color change from yellow to red (see Scheme 2).[25,26]

The anion sensing ability is reflected in quantitative terms in the UV-vis absorption spectra of receptors **1** and **2**. The UV-vis spectra of thiourea **1** and urea **2** changed dramatically on addition of the fluoride ions. Figure 4 and 5 shows the absorption spectra of **1** and **2** in the presence of the fluoride ions. On addition of fluoride ions, the characteristic absorption peaks of **1** at 346 nm decreased gradually with a



Scheme 2. The interaction of receptor with fluoride.

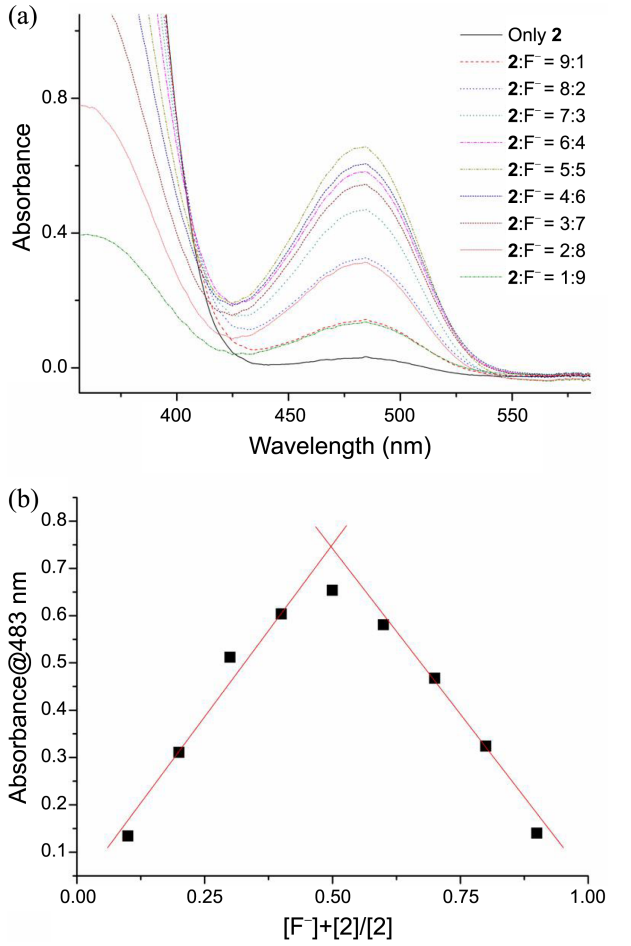


Figure 5. (a) The stoichiometry of the complex between **2** (2×10^{-3} M) and F^- (2×10^{-3} M) in DMSO solution. (b) The stoichiometry analysis of **2**-F^- by job's plot analysis.

strong red shift and a new peak at 417 nm (Fig. 4(a)) was produced. At the same time a clear isobestic point at 304 nm and 379 nm were observed for **1**. The satisfactory result of non-linear curve fitting confirmed that **1** and the fluoride ion formed a 1:1 complex (the non-linear curve of molar absorbance at 417 nm *vs.* the equivalent of the fluoride ion has been inserted in Fig. 4(b)). In addition, the continuous variation method was used to determine the stoichiometric ratios of receptor **2** and the fluoride ion. Figure 5 shows the receptor **2**-F^- ion Job plot of the 483 nm bond absorption *vs.* the mole fraction of the fluoride ion for a series of solutions in which the total concentration of **2** and the fluoride ion was constant, with the mole fraction of the fluoride ion was continuously varied. The result illustrates that the receptor **2**-F^- ion complex concentration peaked molar fraction of **2** of about 0.50 (inserted in Fig. 5(b)), indicating that the receptor formed a 11 complex with the sensitive fluoride ion.

The binding constant could be calculated from the absorption spectral data by the non-linear least-square analysis.[27] The obtained binding constants were listed in Table 1. The selectivity trend shown by receptors was as following: fluoride > acetate > benzoate >> other anions. Receptors displayed the strongest binding afnity toward F^-, which

Table 1. Binding constants ($\log K_a$, M^{-1})[a] of receptors with different anions in DMSO at 298 K

Anions[b]	**1** ($\log K_a$)	**2** ($\log K_a$)
F^-	7.73	ND[c]
AcO^-	7.13	5.01
Benzoate	5.57	4.38
Other anions	NDC[d]	NDC[d]

[a]Values of $\log K_a$ were determined by UV-vis titration spectra. [b]All the anions existed at their TBA salts. [c]Not calculated because stoichiometry analysis of **2**-F^- by job's method. [d]Almost no visible spectral changes were observed.

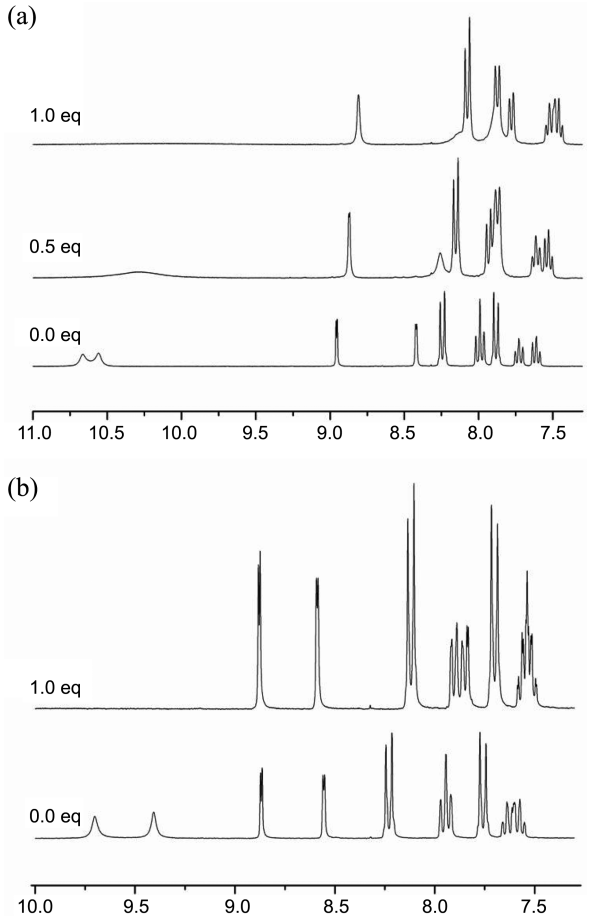


Figure 6. Partial ^{1}H NMR spectra of (a) receptor **1** and (b) receptor **2** in DMSO-d_6 recorded with increased amounts of TBAF, respectively.

could be rationalized by its highest electronegativity.

^{1}H NMR Titrations of Receptors. In general, the chemical shift of a proton moves downfield upon hydrogen bonding. To investigate the relative preference among the binding abilities of the receptors for the fluoride ion, ^{1}H NMR titration experiments were performed in DMSO-d_6. The ^{1}H NMR spectrum of **1** showed N-H protons at 10.56 and 10.66 ppm (Fig. 6(a)). When 0.5 equiv. of fluoride was added to the solution of **1**, its NMR spectrum changed dramatically. The two amide (N-H) proton signals became broader, and its proton signals moved to a downfield position (at 10.30 ppm) due to the interactions between thiourea of **1** and the fluoride

Table 2. Calculation of binding energies (eV)[a] of receptors and anions

Compounds	Binding Energy (eV)
1+F^-	4.77
1+AcO^-	2.95
2+F^-	4.63
2+AcO^-	2.93

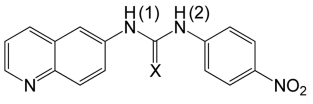
[a]The reaction energies are obtained by binding energy = (L mp2 + Anion mp2) – Anion mp2 – L mp2.

ion. In Figure 6(a), the addition of 1.0 equiv. F^- ions, which caused the disappearance of the N-H protons thiourea moiety, was due to the hydrogen bonds.

The ^{1}H NMR spectra of **2** were also changed selectively in the presence of the fluoride ion (Fig. 6(b)). Upon the titration of 1.0 equiv. fluoride ion, the two amide N-H signals (9.40 and 9.70 ppm) completely disappeared. These results indicated that the strong hydrogen bonds were formed between the amide N-H and the fluoride ion.

Theoretical Investigations on the Structure. The geometries of all species, both reactants and products, involved in the equilibria of **1** and **2** were optimized in the gas phase at the HF/3-21G* level using the Gaussian 98 quantum mechanical calculation program. The optimized structures of receptors **1** and **2** with F^- are represented in Figure 7. The energy was calculated at the HF/3-21G* theoretical level and the electronic correlation effect was taken into account through Møller-Plesset second-order perturbation theory (MP2) single point calculations, designated as MP2/3-21G*//3-21G*. In addition, the calculations for the binding energies of the receptors and anions (F^- and AcO^- ions) are summarized in Table 2. The calculated binding energies for receptor **1** with F^- or AcO^- were relatively larger than those of receptor **2**. Although the sulfur containing amide generally forms weaker hydrogen bonds, receptor **1** should act as a better receptor for F^- at room temperature. The HF/3-21G* calculated results suggest that the N-H(2)···F^- hydrogen bond (*ca.* 1.022 Å) of **1** was much shorter than the N-H(2)···F^- hydrogen bond (*ca.* 1.035 Å) of **2** (Table 3). The shorter H···F^- interatomic distances would be more susceptible to deprotonation in the presence of excess F^-.[28-30] Therefore, the optimized geometries implied that deprotonation sites of one of the two N(H) hydrogen atoms of the thiourea/urea derivatives could be tuned through the remote substituent effect.

Table 3. Computed distances[a] of NH···anion hydrogen bonds from HF/3-21G* calculations



	H(1)···F^-	H(2)···F^-	H(1)···AcO^-	H(2)···AcO^-	H(2)···N
1	1.947	1.022	ND[b]	ND[b]	1.499
2	1.935	1.035	1.738	1.719	1.466

[a]The unit of the computer distances is Å. [b]Not calculated.

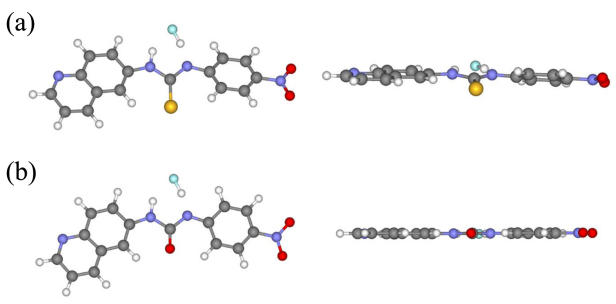


Figure 7. HF/3-21G*-optimized geometrical structures of (a) **1** with F^-, and (B) **2** with F^- at HF/3-21G* levels (color key: red = oxygen; blue = nitrogen; yellow = sulfur; greenish-yellow = fluoride).

Conclusion

Two new simple anion receptors (thiourea **1** and urea **2**) were synthesized by the reaction of 6-aminoquinoline with either 1-isothiocyanato-4-nitrobenzene (receptor **1**) and 1-isocyanato-4-nitrobenzene (receptor **2**). The receptors exhibited particularly good selectivity for fluoride ion and were shown to bind anions in a 1:1 stoichiometry based, according to UV-vis titration results. ^{1}H NMR titration experiments with F^- indicated that fluoride anion has strong hydrogen bonding interactions with the N–H of the amide The obvious colorimetric changes that accompanied this process were due to the fluoride ion-induced, hydrogen bonding and deprotonation of the N–H acidic proton of the receptors. Therefore, these results confirmed the value of these receptors as powerful colorimetric sensors for F^- with a promising potential in practical applications. Development of colorimetric chemosensors capable of working in aqueous environment is ongoing in our laboratory and relevant results will be reported in due course.

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