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Urea/thiourea-based colorimetric chemosensors for the biologically important ions: efficient and simple sensors

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Abstract—Some colorimetric anion sensors have been synthesized where 4-nitrophenyl was treated as a signaling unit and urea/thiourea moieties as binding sites. The receptors, effectively and selectively, recognized the biologically important F^- and carboxylate anions from other anions such as Cl^- and Br^- in DMSO.

1. Introduction

The development of simple receptors capable of recognizing biologically relevant anions such as fluoride, chloride, phosphate, and carboxylate has attracted considerable interest in the recent past.[1] The design of these receptors has been focused on having the ability to selectively recognize and sense the biologically important anions through the naked eye, electrochemical, and optical responses.[2] While the incorporation of fluorescent chromophores into the receptor has gained considerable attention owing to their high sensitivity and easy detection for a long time,[3] the investigation of anion-selective receptors based on color chromophores has just recently begun.[4] In particular, the development of colorimetric anion sensing is even more important and useful since the colorimetric anion sensing system would allow the so-called 'naked-eye' detection of anions without use of any spectroscopic instrumentation, being simple and convenient for detection. Such receptors would be more valuable if they can be obtained by a simple synthetic method.[5]

Many chemical sensors follow the approach of the covalent attachment of signaling subunits and binding sites.[6] Hydrogen-bonding sites typically used in chromogenic or fluorogenic chemosensors are ureas, thioureas, calyx[4]pyrroles, sapphyrins, and amides.[7] Among them, the urea or thiourea groups have been often focused as anion binding sites, because the hydrogen-bonding ability of these functional groups can result in quite stable complexes strongly hydrogen-bonded with biologically important anions such as acetate, phosphate or chloride, and because they can be often easily synthesized from commercially available reagents by a single-step procedure.[7a–c] Therefore, a variety of receptors containing one or more urea subunits have been designed and tested for anion recognition and sensing over the past years. Especially, several urea or thiourea derivatives connected with a series of spacer units including cyclic structures (naphthalene, anthracene etc.) have been synthesized and proved to be very efficient for the anion sensors.[8] Very recently, Jose et al. have reported the new colorimetric receptors by introducing two phenylurea/phenylthiourea into an anthraquinone spacer acting as a signaling subunit.[9] The thiourea receptor has shown the efficient colorimetric sensing, while the urea one needs a certain temperature (above 60 °C) to display the colorimetric action. This result led us to suggest that if the acidity of the urea/thiourea increases, the colorimetric receptors will be more efficient even at room temperature. Therefore, we have planned to design new urea/thiourea with a nitrophenyl group as a signaling group to enhance both hydrogen-bond donor tendency and acidity and to be well known as a chromophore for color change. We have attached two *p*-nitrophenylurea groups or two *p*-nitrophenylthiourea groups to a simple 4,5-dimethyl-1,2-diaminobenzene ring, in which the methyl groups help easy observation of ^1H NMR spectral shift. Anion binding properties of the new urea/thiourea anion sensors were investigated by UV–vis spectroscopy and color changes. As expected, they have shown a unique color change and UV–vis absorption peak in the presence of

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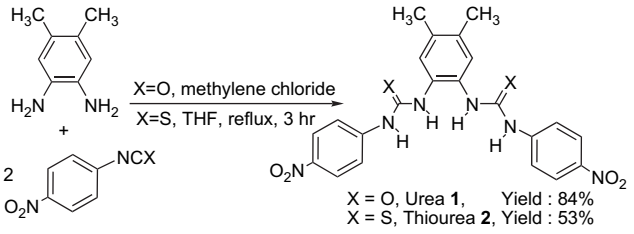
fluoride or acetate ions. During the preparation of the manuscript, we found a related publication where bis-urea compounds based on *ortho*-phenylenediamine function have been used as carboxylate anion receptors. The recognition was monitored by NMR method, however, there were no results and discussion for the color changes or UV–vis observation.[10]

We report herein on novel colorimetric receptors for selective fluoride or acetate ion sensing containing nitrophenyl group as chromogenic signaling subunit and urea/thiourea as binding sites. The anion recognition via hydrogen-bonding interactions can be easily monitored by anion-complexation induced changes in UV–vis absorption spectra and with the naked eye. Moreover, the hydrogen bonds between N-H of the urea/thiourea and fluoride or carboxylate ions are described on the basis of the ^{1}H NMR experiments, and a feature of the binding mode is predicted on the basis of ab initio calculations.

2. Results and discussion

Urea **1** and thiourea **2** were synthesized using the one-step reaction of 4,5-dimethyl-1,2-phenylenediamine and 4-nitrophenyl isocyanate or 4-nitrophenyl isothiocyanate in a reasonably good yield (Scheme 1). Urea **1** was immediately precipitated when 4,5-dimethyl-1,2-phenylenediamine and 4-nitrophenyl isocyanate were mixed together in methylene chloride at room temperature. Thiourea **2** was obtained from the reflux condition in THF, meaning that 4-nitrophenyl isothiocyanate is less reactive with 4,5-dimethyl-1,2-phenylenediamine than 4-nitrophenyl isocyanate.



Scheme 1. Synthesis of the receptors **1** and **2**.

The selective recognition of urea **1** and thiourea **2** with F^- over other halides such as Cl^- and Br^- was evident in ^{1}H NMR titration experiment. ^{1}H NMR spectrum of urea **1** in DMSO-d_6 showed N-H protons at 9.79 and 8.16 ppm.

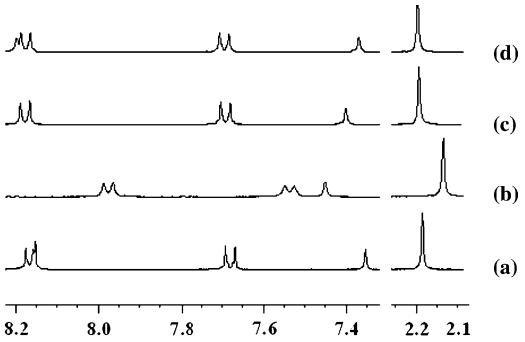


Figure 1. Partial ^{1}H NMR spectra of urea **1** (2.5×10^{-3} M) in DMSO-d_6. (a) **1** only; (b) **1**+2 equiv F^-; (c) **1**+2 equiv Cl^-; (d) **1**+2 equiv Br^-.

Aromatic protons and methyl group were shown at 8.18, 7.68, and 7.36 ppm and at 2.19 ppm, respectively. ^{1}H NMR peaks of urea **1** were changed dramatically in the presence of 2 equiv of F^- whereas there were no significant spectral changes in the phenyl and methyl proton regions for the addition of Cl^- and Br^- (Fig. 1). Two N-H proton peaks disappeared in the presence of F^- and shifted to the downfield in the presence of Cl^- or Br^-. The ^{1}H NMR peaks at 8.18 and 7.68 ppm from nitrophenyl group and a single peak at 2.19 ppm from methyl moved to the upfield, and another singlet (7.36 ppm) from the phenylene moved to the downfield with the addition of 2 equiv of F^- ion as shown in Figure 2a.

The ^{1}H NMR spectra of thiourea **2** were also changed selectively in the presence of F^-. By the titration of F^-, all proton signals from phenylene group (8.14, 7.83, and 7.23 ppm) as well as methyl group (2.22 ppm) shifted to the upfield (Fig. S1). Line broadening of the peaks was observed in the addition of F^- ion. It is clear that F^- binds to four urea N-H protons in both urea **1** and thiourea **2** since the N-H signals were all broadened in the presence of small amounts of F^-. When more than 1 equiv of F^- was added, all N-H peaks disappeared. Addition of acetate ion also developed some changes in the ^{1}H NMR spectra of urea **1** as well as thiourea **2**. The changes by acetate ion in ^{1}H NMR spectra of thiourea **2** were similar to those caused by F^-. On the other hand, in urea **1** case, the chemical shift changes by acetate anion were smaller when compared to those caused by F^- and were not observed after the addition of 1 equiv of acetate anion in the titration (Fig. 2b).

Based on the NMR experiment result for qualitatively selective recognition of some anions by the host molecules, urea **1** and thiourea **2**, further study of the anion recognition has

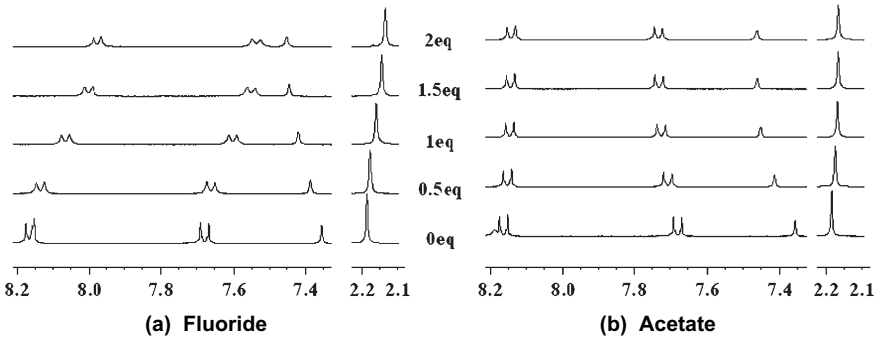


Figure 2. Titration of a 2.5×10^{-3} M solution of urea **1** in DMSO-d_6 with (a) F^- and (b) CH_3COO^- ions.

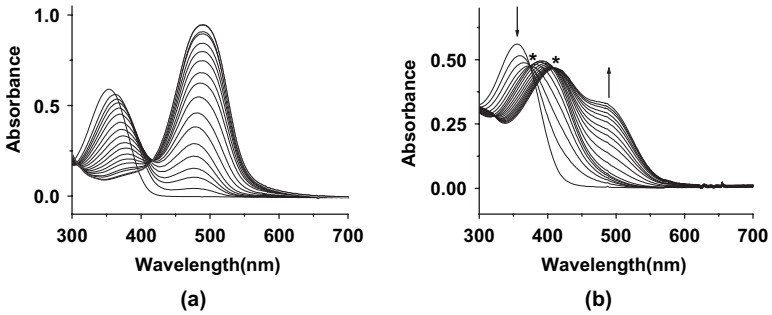


Figure 3. UV–vis spectral changes observed for **1** and **2**, upon addition of fluoride anion in DMSO at room temperature. (a) Urea **1** (2.5×10^{-5} M) with F^- (0–105 equiv) and (b) thiourea **2** (3.4×10^{-5} M) with F^- (0–3.4 equiv).

been carried out. The remarkable preference in binding ability of urea **1** and thiourea **2** for F^- was observed with clear color change *even at room temperature*, unlike the phenylurea receptor with an anthraquinone spacer designed by Jose et al.,[9] and monitored with UV–vis spectroscopy. The UV–vis spectra of urea **1** and thiourea **2** changed dramatically when small amounts of F^- ions were added whereas there were no UV–vis spectral changes upon the addition of up to 250 equiv of Cl^- or Br^- ions. In the course of addition of F^- ion to urea **1**, a new peak at λ_{max}=488 nm was developed and the isosbestic point was observed at 416 nm as shown in Figure 3a.

The more drastic UV–vis spectral change was observed for thiourea **2** as shown in Figure 3b. Again, a new peak was shown at λ_{max}=488 nm. There are two isosbestic points: one at 374 nm and the other at 409 nm. A maximum intensity of ~90% at 488 nm was obtained for thiourea **2** when less than 10 equiv of F^- were added, whereas ~70 equiv of F^- were needed for urea **1** to obtain the same intensity. This result shows that F^- binds with thiourea **2** more tightly than with urea **1**, indicating stronger hydrogen bonds of acidic N-H groups in thiourea **2**.

Figure S2a shows that UV–vis absorption of urea **1** also changes in the presence of acetate ion. The λ_{max} slowly moved from 354 to 366 nm when 10 equiv of acetate ion were added. Addition of more than 10 equiv of acetate ion did not give any further spectral changes. The presence of one isosbestic point at 359 nm implies that two species, **1** and **1**-acetate, are present in equilibrium, and the analysis of the set of UV–vis spectra indicates the 1:1 complex with a complexation constant $K=1.1(\pm0.1)\times10^5$.[11]

The UV–vis spectrum of thiourea **2** showed dramatic changes in the course of titration with acetate ion as shown in Figure S2b. The UV–vis spectral change of urea **1** with acetate ion was significantly different from that with fluoride ion. However, the change of thiourea **2** with acetate was similar to that with fluoride ion. Even though the binding constant for complexation of thiourea **2** with acetate was not obtained, it is expected to be the same order of magnitude (~10^5) since the binding constant for the urea with F^- was reported to be about half of that for the thiourea analogue due to the less acidic protons.[9]

Pfeffer group reported complexation constants of some thioureas with acetate ion where the log *K* values were 3.6 for the aliphatic thiourea and 3.9–4.0 for aromatic thioureas, and explained the difference in terms of the acidity of thiourea protons.[2e,2f,4a] Other studies also reported that thiourea-based anion sensors have the binding constant values of the order of magnitude (~10^5)[4f,12] with acetate anion, which is comparable to our result.

The anion recognition is also detectable at room temperature with naked eyes as shown in Figure 4. Again, Cl^- and Br^- did not give any noticeable color changes in the DMSO solution of urea **1** and thiourea **2**. For urea **1**, only F^- gave significant color changes to reddish orange. Acetate ion made the solution turn pale yellow, but the color change was not noticeable at low concentration with naked eyes. Color change of thiourea **2** was much more sensitive to F^- than urea **1**. One equivalent of F^- was enough to recognize color change from colorless to yellow with naked eyes. More addition of F^- changed the color to reddish orange. In contrast to urea **1**, the solution of thiourea **2** with acetate ion turned yellow at low concentration of acetate ion and reddish orange at high concentration.

Two isosbestic points in UV–vis spectra and two different colors, yellow and reddish orange, in naked-eye detection

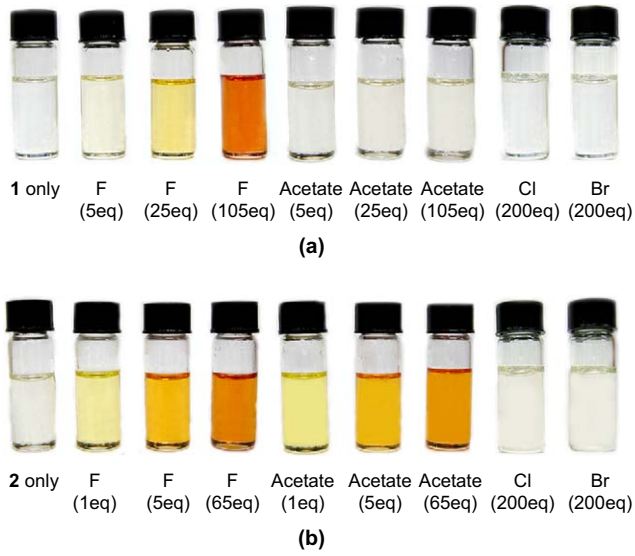


Figure 4. Color changes observed for **1** and **2** in DMSO upon the addition of anions as tetraethylammonium salts at room temperature. (a) Urea **1** (2.5×10^{-5} M) and (b) thiourea **2** (2.5×10^{-5} M) (number of equivalents in parenthesis).

during the host–guest complexation suggest the following equilibria for the interaction between urea/thiourea and F^- as Fabbrizzi et al. proposed.[2g,2h,4c,4d]

Equilibrium I: $RH + L^- \leftrightarrows RH\cdots L^-$

Equilibrium II: $RH\cdots L^- + L^- \leftrightarrows R^- + LHL^-$

The first equilibrium is accomplished for the complexation between the host (RH=urea **1**/thiourea **2**) and the guest (L^-=anion). If there are more free anions, the host molecules can be deprotonated and exist in the form of an anion R^- as shown in equilibrium II. The equilibrium constants of these two processes would be mainly dependent on the binding constant value of the host–guest complex and the acidity of host or the basicity of anions.

For both urea **1** and thiourea **2**, the host–guest complex is responsible for ~370 nm peak in the UV–vis spectra or pale yellow color in the naked-eye detection. On the other hand, the new anion species R^-, in the equilibrium II, are responsible for the 488 nm peak in the UV–vis spectra and reddish orange color in the naked-eye detection. Both urea **1** and thiourea **2** are believed to reach the equilibria I and II with F^- probably due to strong hydrogen-bonding interaction between urea/thioura N-H and F^-, which eventually generates a highly stable anion species FHF^- in the equilibrium II.

To support the suggested equilibrium profile, the geometries of all species involved in equilibria I and II were optimized in gas phase at the HF/6-31+G(d) level using ab initio calculation (Fig. 5). All four protons of urea/thiourea are directed toward anion ligands but each hydrogen-bond distance is different as shown in Table 1. Two protons (H(3) and H(4)) connected to nitrophenyl group have much shorter distances to the anions than the other N-H protons. The hydrogen-bond distances increase as the sizes of the anion ligands from fluoride to bromide increase. The two oxygen

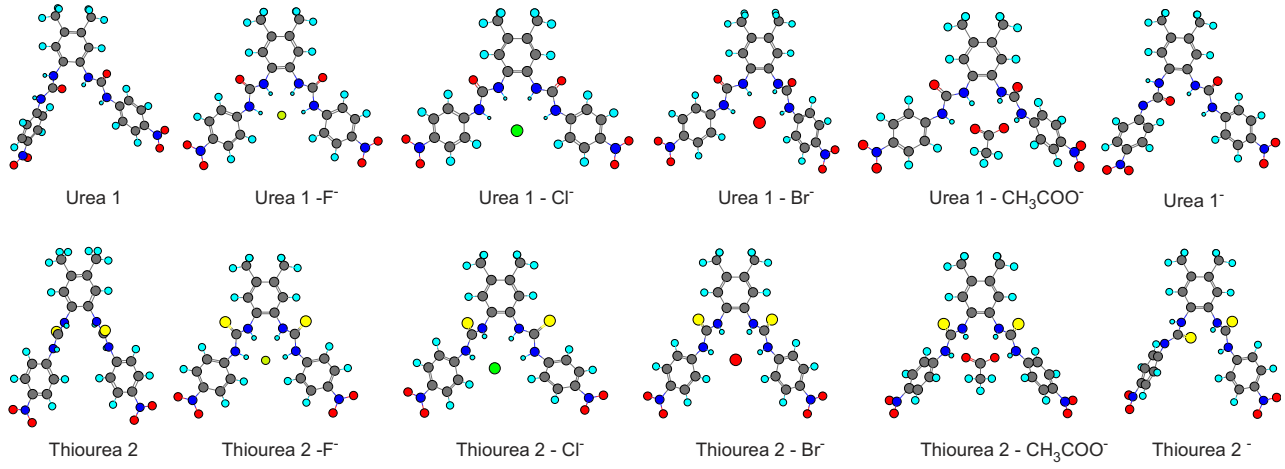
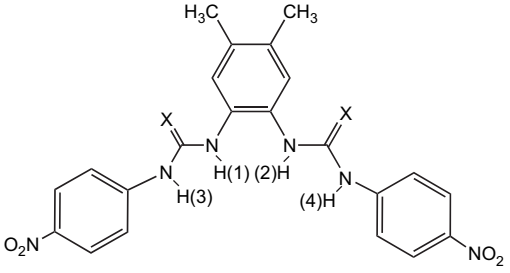


Figure 5. Optimized geometries from ab initio HF/6-31+G(D) calculations.

Table 1. Computed distances[a] of $NH\cdots L^-$ hydrogen bonds from ab initio HF/6-31+G(D) calculations



Ligand	H(1)···L^-	H(2)···L^-	H(3)···L^-	H(4)···L^-
Receptor: urea **1** (X=O)				
F^-	1.924	1.919	1.753	1.755
Cl^-	2.614	2.637	2.333	2.336
Br^-	2.655	2.479	2.448	2.509
CH_3COO^-[b]	2.025(O1)	2.155(O2)	1.836(O1)	1.870(O2)
Receptor: thiourea **2** (X=S)				
F^-	2.056	2.056	1.649	1.649
Cl^-	2.570	2.992	2.289	2.321
Br^-	2.575	2.577	2.536	2.535
CH_3COO^-[b]	1.957(O1)	1.957(O2)	1.910(O1)	1.910(O2)

[a] The unit of the computed distances is Å.
[b] Two oxygen atoms (O1 and O2) of CH_3COO^- form hydrogen bonds with the receptors where O1 is hydrogen-bonded to H1 and H3 and O2 to H2 and H4.

atoms of CH_3COO^- effectively form four hydrogen bonds (two per oxygen atom) with each receptor and their hydrogen-bond distances are within the typical hydrogen-bond distance ranges between 1.86 and 2.16 Å. In general, the anions are well-positioned into the hydrogen-bond cage in the complexes through favorable hydrogen-bonding interactions. The reaction energies between the reactants and the products were also calculated based on the optimized geometries using the density functional theory at the B3LYP/6-31G+(d)//HF/6-31+G(d) level (Table S1). The preference of both urea/thiourea receptors for the anions can be ordered as follows: $F^->CH_3COO^->Br^->Cl^-$. In the equilibrium II, thiourea **2** is more favorable than urea **1** for all anions mainly due to the higher acidity of thiourea protons.

Deprotonation of nitrophenyl connected urea protons are well known and the resulting R^- is a push–pull chromophore, which is responsible for the 488 nm peak in the UV–vis and the development of the reddish orange color.[4] Acetate ion is basic enough to deprotonate the protons of thiourea **2**, but is not basic enough to deprotonate those of urea **1**. Therefore, only the equilibrium I exists between urea **1** and acetate ion, and the resulting complexation constant was found to be $K=1.1(\pm0.1)\times10^5$ with high accuracy. From the computational results, the value of the complexation constant for thiourea **2**-F^- is expected to be more or less the same as that for urea **1**-F^-.

3. Conclusion

We have developed new colorimetric anion sensors having both 4-nitrophenyl as a signaling unit and urea/thiourea moieties as binding sites, and investigated their affinity and selectivity to the halide and acetate anion experimentally and theoretically. The receptors effectively and selectively recognize the biologically important F^- and carboxylate anions over other anions such as Cl^- and Br^- in DMSO. More importantly, the new colorimetric chemosensors for anions have displayed naked-eye detection *at room temperature*, unlike the phenylurea receptor with an anthraquinone spacer designed by Jose et al.[9] In addition, the NMR and ab initio calculations are in good agreement with the color changes. Therefore, it is believed that 4-nitrophenylurea and -thiourea binding sites attached to a simple benzene ring are suitable colorimetric reagents for fluoride and carboxylate sensing. We have also shown that even simple chromophores such as cheap and easy-to-make anion receptors containing hydrogen-bonding donor groups can operate as efficient colorimetric sensors for the naked-eye detection of anions.

4. Experimental

4.1. General

All reagents were purchased from Aldrich and used without further purification. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-AL400 spectrometer, operating at 9.39 T. UV–vis spectra were obtained using a Cary 3 spectrophotometer with a quartz cuvette (path length=1 cm). IR spectra were measured on a BIO RAD FTS 135 spectrometer as KBr pellets. Elemental analysis for carbon, nitrogen, and hydrogen was carried out by using an EA1108 (Carlo Erba Instrument, Italy) in the Organic Chemistry Research Center of Sogang University, Korea.

4.2. Synthesis of *N*,*N*′′-1,2-(4,5-dimethylphenylenebis-[*N*′-*p*-nitrophenylurea]) (1) and *N*,*N*′′-1,2-(4,5-dimethylphenylenebis[*N*′-*p*-nitrophenyl(thiourea)]) (2)

To a methylene chloride (5 ml)/THF (3 ml) solution of 4-nitrophenyl isocyanate (0.37 g, 2.2 mmol), 4,5-dimethyl-1,2-phenylenediamine (0.14 g, 1.0 mmol) in methylene chloride (3 ml) was added slowly while being stirred vigorously. The orange solid (**1**) was immediately formed, filtered, and dried (yield 84%). Anal. Calcd for $C_{20}H_{20}N_6O_6$, **1**: C, 56.89; H, 4.34; N, 18.10. Found: C, 56.82; H, 4.46; N, 18.33%. ^1H NMR (DMSO-d_6) δ 9.79 (s, 2H), 8.18 (d, 4H, J_3=9.3 Hz), 8.16 (s, 2H), 7.68 (d, 4H, J_3=9.3 Hz), 7.36 (s, 2H), 2.19 (s, 6H). ^{13}C NMR (DMSO-d_6) δ 152.6, 146.4, 140.8, 132.6, 128.4, 125.4, 125.0, 117.3, 19.1. IR (KBr): 3340, 1678, 1504, 1327 cm^{-1}.

4,5-Dimethyl-1,2-phenylenediamine (0.14 g, 1.0 mmol) in THF (3 ml) was added to a THF (5 ml) solution of 4-nitrophenyl isothiocyanate (0.38 g, 2.1 mmol). The mixture was stirred at reflux for 3 h. After the solution was concentrated to 1 ml, methylene chloride and hexane were gradually added until precipitate was formed. The light yellow solid (**2**) was filtered and dried (yield 53%). Anal. Calcd for $C_{22}H_{20}N_6O_4S_2$, **2**: C, 53.21; H, 4.06; N, 16.92; S, 12.91. Found: C, 53.15; H, 4.15; N, 17.01; S, 12.75%. ^1H NMR (DMSO-d_6) δ 10.44 (s, 2H), 9.52 (s, 2H), 8.14 (d, 4H, J_3=8.8 Hz), 7.83 (d, 4H, J_3=8.8 Hz), 7.23 (s, 2H), 2.22 (s, 6H). ^{13}C NMR (DMSO-d_6) δ 179.7, 145.8, 142.3, 135.1, 131.4, 128.8, 124.1, 121.5, 19.0. IR (KBr): 3320, 3272, 1507, 1347, 1113 cm^{-1}.

4.3. UV–vis and NMR titrations

UV–vis titrations were performed on $1–5\times10^{-5}$ M solutions of urea **1** or thiourea **2** in DMSO. Typically, aliquots of freshly prepared Et_4NX (X=F^-, Cl^-, Br^-, and CH_3COO^-) standard solutions ($10^{-1}–10^{-3}$ M in DMSO) were added and the UV–vis spectra of the samples were recorded. ^1H NMR titrations were carried out in DMSO-d_6.

4.4. Ab initio calculation

The geometries of all species such as the reactants and products involved in the equilibria I and II were optimized in gas phase at the HF/6-31+G(d) level using the GAMESS quantum mechanical calculation program.[13] The computed geometrical quantities are shown in Table 1. The reaction energies for both equilibria were also calculated based on the above optimized geometries using the density functional theory at the B3LYP/6-31G+(d)//HF/6-31+G(d) level. The reaction energies were simply obtained by taking the energy difference between the reactant and the product molecules. The energetic results are shown in Table S1.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.07.081.

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11. One of the reviewers has been interested in the *K* value for **1** with phosphate ion and comparison of its *K* value and those values obtained with the similar receptor (1-(4-nitrophenyl)-3-{2-[3-(4-nitrophenyl)ureido]cyclohexyl}urea=**3**) reported in Ref. 7i. Our preliminary *K* value ($\sim 2\times10^5$) for **1** with phosphate ion was found to be two orders of magnitude bigger than that (log K=2.96) for **3** with phosphate ion as shown in Ref. 7i. This difference could come from the structure difference between **1** and **3**. More details will be explained in the next paper.
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