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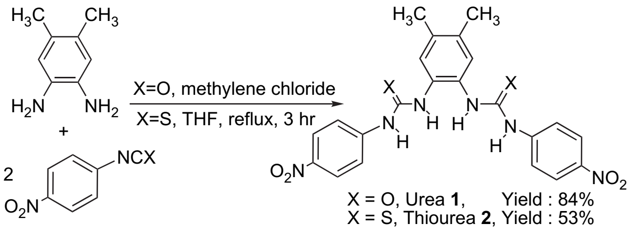
fluoride or acetate ions. During the preparation of the manuscript, we found a related publication where bis-urea compounds based on *ortho*-phenylenediamine function have been used as carboxylate anion receptors. The recognition was monitored by NMR method, however, there were no results and discussion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

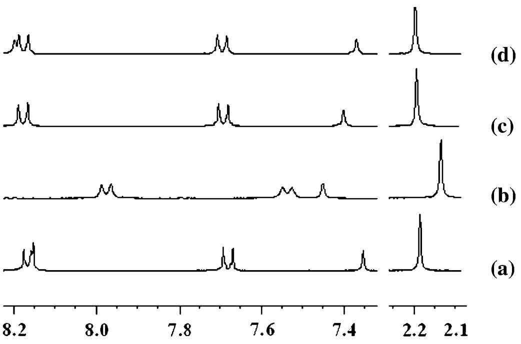
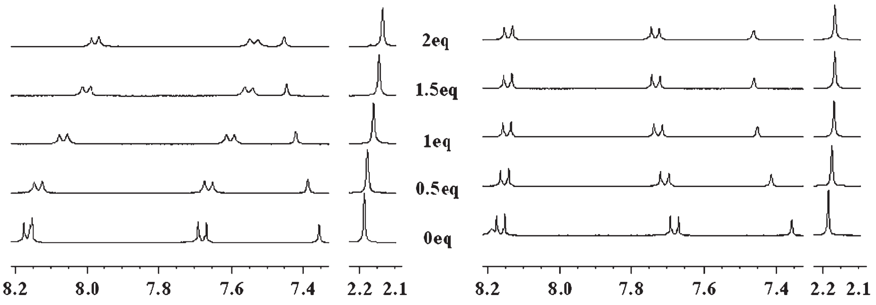


Figure 1. Partial ^{1}H NMR spectra of urea **1** (2.5×10^{-3} M) in DMSO-d_6. (a) **1** only; (b) **1**+2 equiv F$^-$; (c) **1**+2 equiv Cl$^-$; (d) **1**+2 equiv Br$^-$.

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



(a) Fluoride **(b) Acetate**

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.