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ORIGINAL PAPER

Study on the Selectivity of Anion Receptors Based on Similar (thio)urea Fragments

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Abstract Three new selective anion receptors containing the (thio)urea binding sites were developed, Indole-3-formaldehyde phenyl-semithiocarbazone, Indole-3-formaldehyde nitrophenyl-semithiocarbazone, and Indole-3-formaldehyde nitrophenyl-semicarbazone, nominated as receptors **1**, **2** and **3**, respectively. Receptor **1** shows high selective recognition for F^- only, while both receptor **2** and receptor **3** containing a *p*-nitro group show high selective recognition for AcO^-. The high selective recognition of these receptors to anions is further investigated by X-ray crystallography diffraction, UV-vis, fluorescence analyses and ^1H NMR. Furthermore, receptor **2** changes from yellow to orange, and receptor **3** darkens when acetate is added, providing a way of detection by 'naked-eye'.

Keywords Fluoride ion · Acetate · Anion recognition · Colorimetric · Naked-eye

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Introduction

With the development of biology and biochemistry, great attention has been paid to some important biological ions, such as F^- and AcO^-, which have significant effect on many metabolic processes [1, 2]. A lack of F^- may cause tooth decay, while an excess of F^- might lead to heart disease and fluorosis [3]. As one of the bases of almost all the creatures, acetate exhibits specific biolochemical behaviors in the enzymes. Also, combined with coenzyme [4], it becomes the key substance in the metabolism of carbohydrate. Consequently, the recognition and sensing of F^- and AcO^- is a very important and interesting subject.

Recently, a great many of anion receptors has been designed and synthesized. Many signals, such as redox potential changes [5], UV–vis spectral changes [6], color changes [7] and emission fluorescence changes [8] have been developed in different methods. Among these methods, much effort has been made in color changes and emission fluorescent changes because they can be observed only by 'naked-eye'. For example, an effective sensor for acetate ion in dry DMSO was reported by J. P. Cheng et al. [9]. Y. Ito et al. reported that a novel Fipronil-based receptor can selectively recognize actetate among a group of anions in DMSO [10]. We found that the phenylhydrazone-based indole receptor was an effective sensor for acetate ion in dry DMSO [11].

Generally speaking, receptors are composed of at least two parts: binding part and chromophore [12]. These two parts are either linked or intramolecularly associated [13, 14], giving a change in the color when the receptor combines with an anion. In this way, we can detect anions without any spectroscopic instruments.

In our work, we have synthesized and investigated three new receptors based on indole derivatives. Although receptor **1** exhibits a selective recognition towards F^-, its sensitivity is not ideal. It does not change its color on the addition

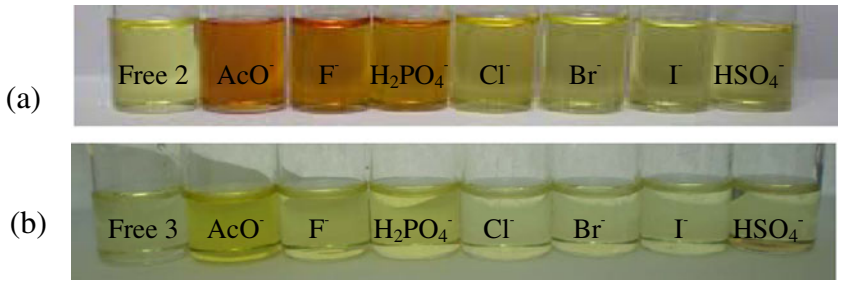


Fig. 1 Color changes of receptors **2** (**a**) and **3** (**b**) in DMSO. [1]=[2]=5.0×10^{-4} M, [anion]=2.5×10^{-3} M, from left to right: free receptor, AcO^-, F^-, $H_2PO_4^-$, Cl^-, Br^-, I^- and HSO_4^-

of F^-, because of lacking a nitro group acting as chromophore. Receptor **2** shows high selective recognition towards AcO^-. The addition of AcO^- results in an obvious change in the visible region of spectrum (slight yellow to orange) which can be detected by the 'naked-eye'. Receptor **3** also shows high selective recognition towards AcO^-, but the color change is not so obvious compared with receptor **2** (see Fig. 1).

Experimental

Materials

All reagents for synthesis obtained commercially were used without further purification. In the titration experiments, 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. Data sets for receptor **3** was measured on a Bruker SMART 1000X diffractometer using graphite monochromated MoKα radiation (λ=0.71073 Å) at 113(2) K. The crystal size is 0.20×0.18×0.12 mm, CCDC is 808045.

General Method

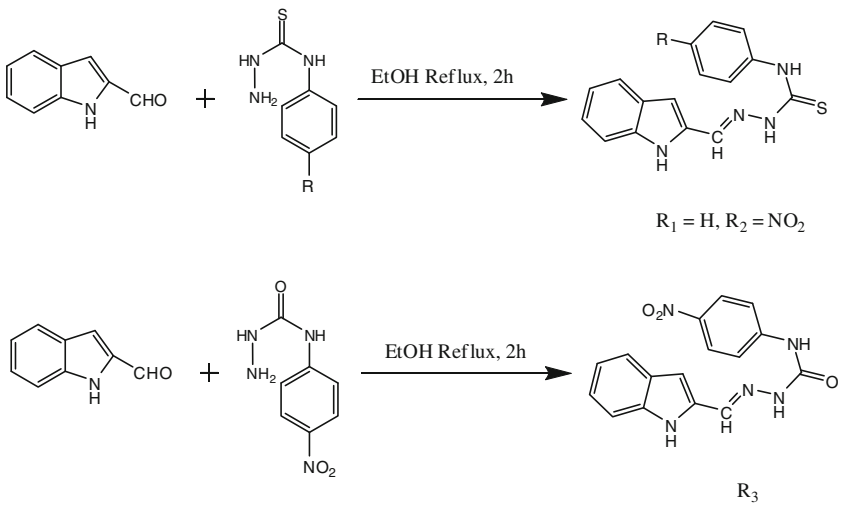
^{1}H NMR spectra were obtained on a Varian UNITY Plus-400 MHZ Spectrometer. ESI-MS was performed with a MARINER apparatus. C, H, N elemental analyses were made on an elementar vario EL. UV-vis spectra were recorded on a Shimadzu UV-2450 Spectrophotometer (Shimadzu 2.1 Apparatus Corp., Kyoto, Japan) with a quartz cuvette (path length= 1 cm) at 298.2±0.1 K. Fluorescent spectra were recorded on a FP-750 fluorescence spectrometer at 298.2±0.1 K and the width of the slits used is 10 nm.

A series of DMSO solutions having the same host concentration and different anion concentrations were prepared respectively. The affinity constants K_s were obtained by the absorption of the series of solutions and the analysis of obtained absorption values using non-linear least square calculation method for data fitting.

Synthesis (see Scheme 1)

Indole-3-Formaldehyde Phenyl-Semithiocarbazone **1**

The receptor **1** was synthesized according to the procedure reported (Scheme 1). Phenylthiosemicarbazide (334 mg, 2 mmol) was added to a solution of indole-3-formaldehyde (145 mg, 1 mmol) in ethanol. After a catalytic amount of



Scheme 1 General synthetic routes to the target receptors

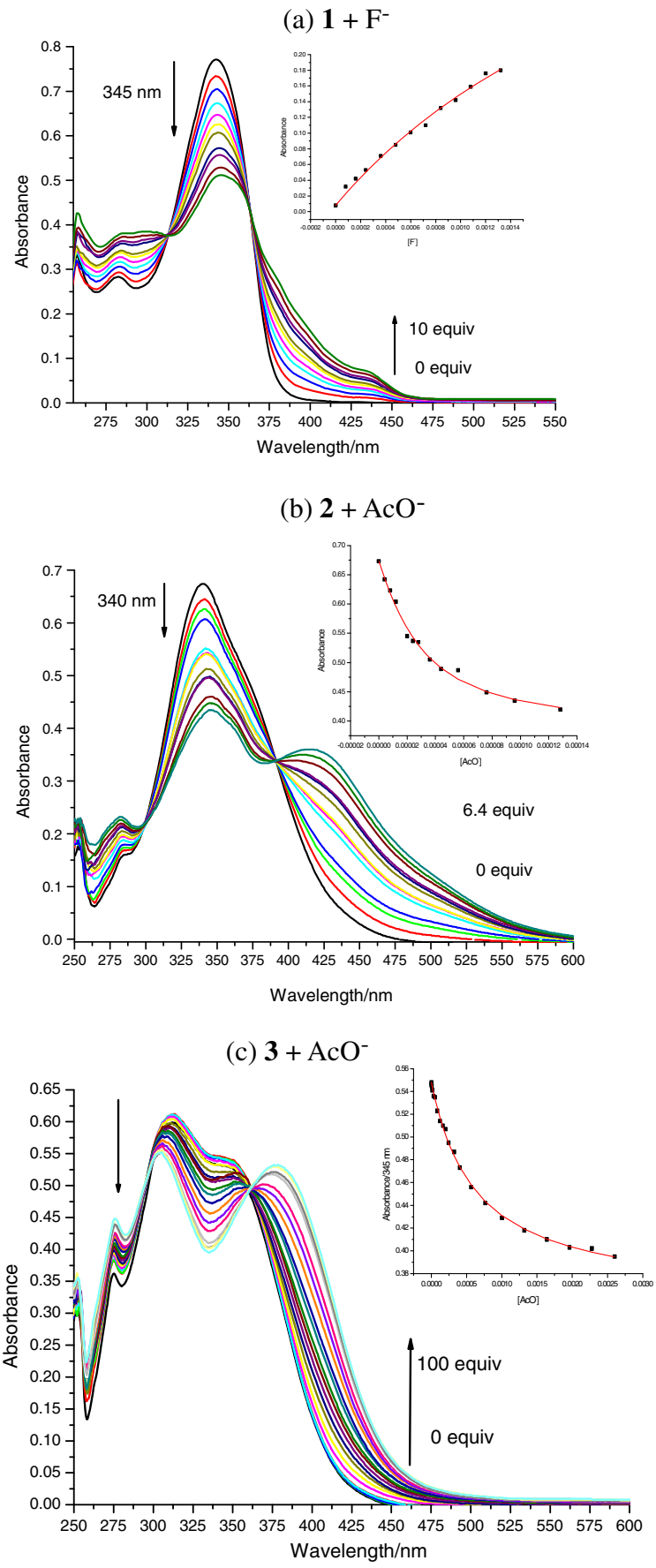


Fig. 2 UV absorption changes of (**a**) **1** with F^-, (**b**) **2** with AcO^- and (**c**) **3** with AcO^- in DMSO, [1]=[2]=[3]=2.0×10^{-5} M

acetic acid was added, the resulting solution was refluxed for 2 h. Then the precipitate was filtered while it was still hot and washed with hot ethanol for several times. Faint yellow solid was obtained in 89 % yield. m. p.: 222–223 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δH:7.16 (m, 3H, Ar-H), 7.35 (m, 3H, Indol-H), 7.61 (d, 2H, Ar-H), 7.89 (d, 1H, Indol-H), 8.20 (d, 1H, Indol-H), 8.38 (s, 1H, C-H), 9.58 (s, 1H, Indol-NH), 11.57 (s, 1H, N-H), 11.66 (s, 1H, N-H). ESI-MS (m/z): calcd. for $C_{16}H_{14}N_4S$ $[M-H]^-$:293.08, found:292.9. Elemental analysis calcd for $C_{16}H_{14}N_4S$: C, 65.28; H, 4.79; N, 19.03, found: C, 65.13; H, 4.99; N, 19.23.

Indole-3-Formaldehyde Nitrophenyl-Semithiocarbazone **2**

Receptor **2** was synthesized according to receptor **1**. Orange solid was obtained in 82 % yield. m. p.: 222–223 °C. ^{1}H NMR400MHz, DMSO-d_6 δH:7.17 (m, 2H, Ar-H), 7.21(d, 1H, Indol-H), 7.95(d, 1H, Indol-H), 7.14(d, 2H, Ar-H), 8.22 (t, 3H, Indol-H), 8.43(s, 1H, C-H), 10.08(s, 1H, Indol-NH), 11.74(s, 1H, N-H), 1.97(s, 1H, N-H)。 ESI-MS(m/z): calcd. for $C_{16}H_{13}N_5O_2S$ $[M-H]^-$:338.07, found:337.8. Elemental analysis calcd for $C_{16}H_{13}N_5S$:C, 56.63; H, 3.86; N, 20.64, found: C, 56.13; H, 3.84; N, 20.42.

Indole-3-Formaldehyde Nitrophenyl-Semicarbazone **3**

Receptor **3** was synthesized according to receptor **1**. Yellow solid was obtained in 85 % yield. m. p.: 249–251 °C. ^{1}H NMR(400 MHz, DMSO-d_6) δH: 7.17 (m, 2H, Ar-H), 7.43 (m, 1H, Indol-H), 7.83 (s, 1H, Indol-H), 7.92 (d, 2H, Ar-H), 8.21 (m, 4H, Indol-H), 9.29 (s, 1H, Indol-NH), 10.68 (s, 1H, N-H), 11.57 (s, 1H, N-H). ESI-MS(m/z):calcd. for $C_{16}H_{13}N_5O_3$ $[M-H]^-$: 322.09, found:321.9. Elemental analysis calcd for $C_{16}H_{13}N_5S$: C, 59.25; H, 4.35; N, 21.59, found: C, 59.43; H, 3.92; N, 21.89.

Results and Discussion

UV-vis Anion Titration Studies

To verify our assumption and further evaluate anion binding behavior of the receptors developed, UV-vis titrations were carried out in DMSO. The solutions of receptors (1.0×10^{-5} M) were added with various kinds of anions including fluoride, chloride, bromide, iodide, dihydrogen phosphate, bisulfate and acetate.

As illustrated in Fig. 2a, an absorption maximum was found at 345 nm. Upon addition of F^-, the peak at 345 nm decreased. And at the same time, two isosbestic points at 313 nm and 370 nm were observed, indicating that receptor **1** and fluoride anion form only one type of complex.

Figure 2b and c show the UV-vis spectral changes of **2** and **3** during the titration with acetate ions. With the increasing concentration of AcO^- ion for **2**, the intensity of the absorption band at 280 nm and 425 nm was gradually enhanced, while the intensity of absorption band at 340 nm decreased correspondingly, and two well-defined isosbestic points at 300 nm and 390 nm appeared. For **3**, the intensity of the absorption band at 377 nm was gradually enhanced, while

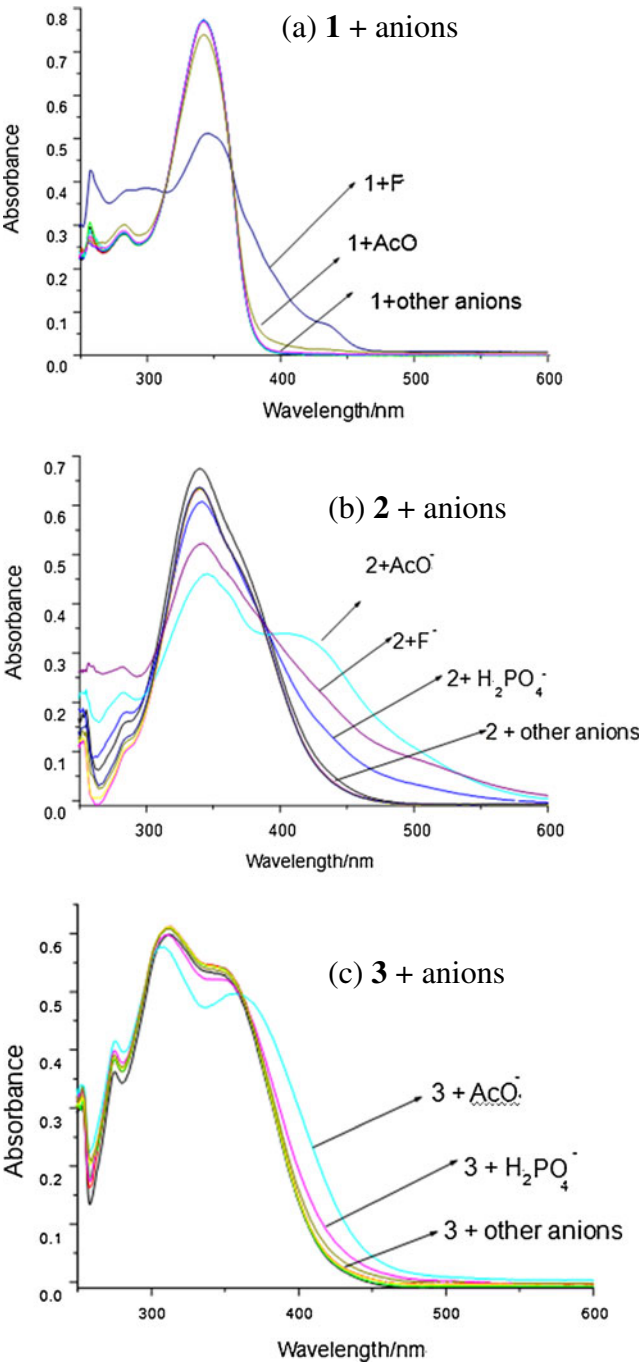
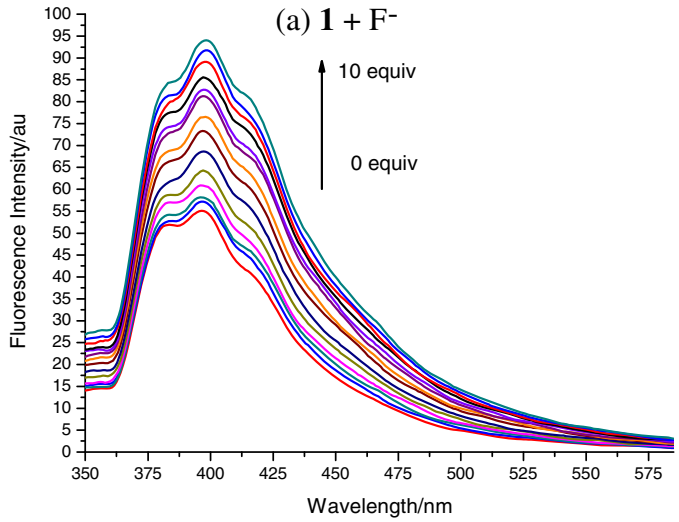
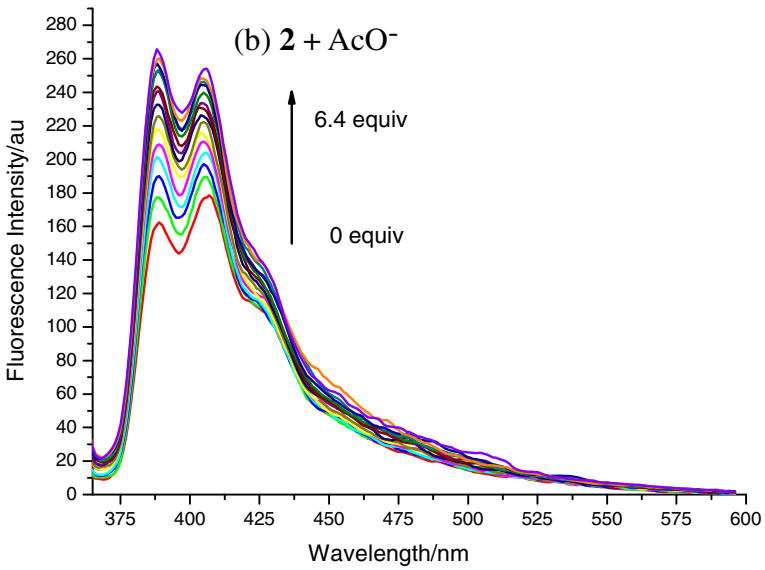


Fig. 3 UV-vis spectrum of receptor (**a**) **1**, (**b**) **2** and (**c**) **3** in the presence of anions in DMSO, [1]=[2]=[3]=2.0×10^{-5} M, [anions]=2.0×10^{-4} M





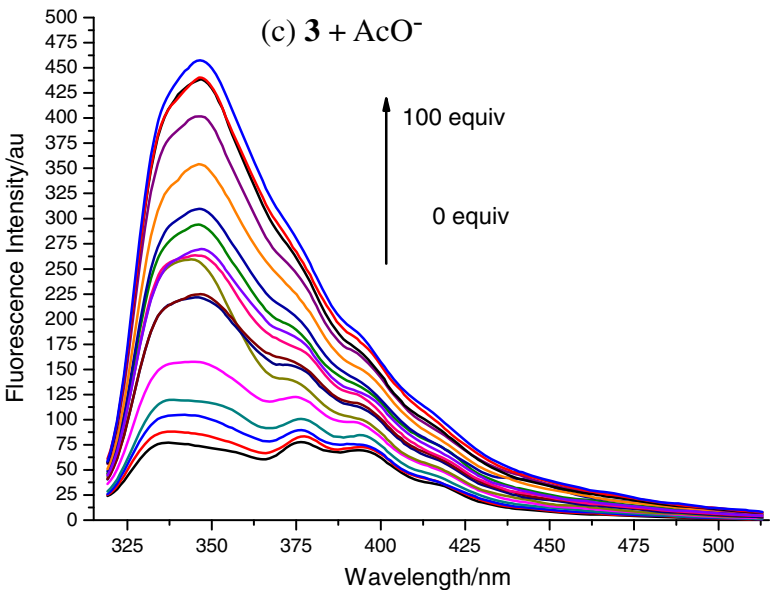


Fig. 4 Fluorescence spectra of (**a**) **1** with F^-, (**b**) **2** with AcO^- and (**c**) **3** with AcO^- in DMSO, [**1**]=[**2**]=[**3**]=2.0×10^{-5} M

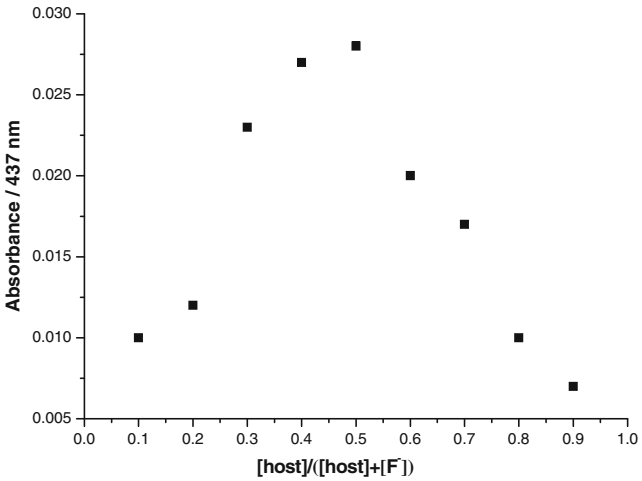


Fig. 5 Job's plot for complexation of **1** with F^- determined by UV-vis in DMSO, [**1**] + [anions]=2.0×10^{-2} M

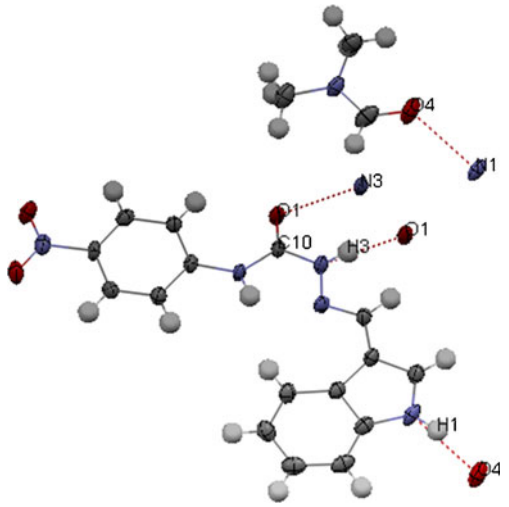


Fig. 6 View of receptor **3** with numbering scheme adopted

the intensity of absorption band at 312 nm decreased accordingly, accompanied by the formation of an isosbestic point at 360 nm. What was observed also indicates that **2** and **3** form only one type of complex with acetate.

Because of their similarity in the structure, receptor **2** and receptor **3** share many features. The two receptors both interact with anionic guests through hydrogen bond, which has an influence on the electronic properties of the chromophore. It lead to a new charge transfer mechanism which is established between the electron rich –NH moiety and the electron deficient $-NO_2$ moiety, along with the color change [15, 16].

In the process, the spectral changes upon the addition of Cl^-, Br^- and I^- were not as clear as that of fluoride or acetate, even when the anions were excessive (see Fig. 3).

Fluorescent Anion Titration Studies

The anion binding behaviors of the three receptors were also investigated by fluorescence titrations in DMSO, and the results were consistent with the UV-vis titrations well. By using receptor **1** as examples, when it was excited at λ= 370 nm, there was an obvious emission band centered at 405 nm. Upon addition of fluoride, there was a significant increase in the emission intensity of **1** (see Fig. 4). According to the literature published before, most of the anion chemosensors, especially the urea- and thiourea-based sensors, are switch-off fluorescent chemosensors, or non-fluorescent sensors. This can be interpreted by the photo-induced electron transfer (PET) quenching mechanism [17, 18] or the heavy atom effect of the sulfur atom. But considering the sensitivity of chemosensing, a switch-on, rather than a switch-off fluorescent sensor would be more preferred [19].

It is evident in Fig. 4a that receptor **1** displays the switch-on reaction towards F^-. This phenomenon may be the result of a binding-induced rigidity of the host molecule [20, 21]. The configuration of free receptor **1** was flexible and could rotate freely. Upon complexation with AcO^- ion, the host molecule **1** was rigidified, which gave birth to a large increase in emission intensity because of inhibition vibrational and totational relaxation modes of nonradiative decay. A similar phenomenon was also observed when adding AcO^- to the solution of receptor **2** and **3**.

Table 1 Association constants for various anions toward receptor **1**, **2** and **3** in DMSO at 298.2±0.1 K, respectively

Anions[a]	AcO^-	$H_2PO_4^-$	F^-	Cl^-	Br^-	I^-	HSO_4^-
K_{ass} (receptor 1)[b]	ND[c]	ND	270.04	ND	ND	ND	ND
K_{ass} (receptor 2)	5.28×10^4	1.67×10^3	1.26×10^4	ND	ND	ND	ND
K_{ass} (receptor 3)	1.63×10^4	1.06×10^3	ND	ND	ND	ND	ND

[a] The anions were added as their tetrabutylammonium salts

[b] K_{ass} was determined in dry DMSO

[c] ND indicated that the spectra showed little or no change with the addition of anion so that the association constants can not be determined by using the spectra

Table 2 Hydrogen bond of receptor **3**

Donor—H… Acceptor	D-H (Å)	H…A (Å)	D…A (Å)	D-H … A (Å)
N1—H1—N3	0.910(13)	2.076(14)	2.6112(14)	116.4(11)
N2—H2—O1^{i}	0.961(14)	1.876(14)	2.8296(13)	171.2(13)
N4—H5—O4^{ii}	0.937(14)	1.863(14)	2.7915(14)	170.6(13)

Discussion

Compared with receptor **2** and **3**, receptor **1**, which lack of the $-NO_2$ group, has been investigated by UV-vis spectral titrations and the fluorescent spectroscopic titrations, rather than the 'naked-eye' detection. Afterwards, we synthesized the two receptors **2** and **3** containing the chromophore, which contributes to the acetate detection by 'naked-eye' (see Fig. 1). Besides, it enhanced the receptors' recognition ability.

This reveals that the introduction of $-NO_2$ group on receptor **2** and **3** plays a positive role in anion recognition.

Determination of the Binding Constant and Stoichiometry

In Fig. 5, Job's plot [22] of receptor **1** and F^- in DMSO shows the maximum at a molar fraction of 0.5. This result indicates that receptor **1** binds F^- anion guest with a 1:1 ratio.

For a complex of 1:1 stoichiometry, the relation in Eq. (1) could be derived easily, where X_0, X_{lim} and X are the absorption intensity of the solution in the absence of guest, presence of the saturated guest, and after addition of a given amount of guest to certain concentration, respectively, C_H or C_G is the concentration of the host or the anion guest

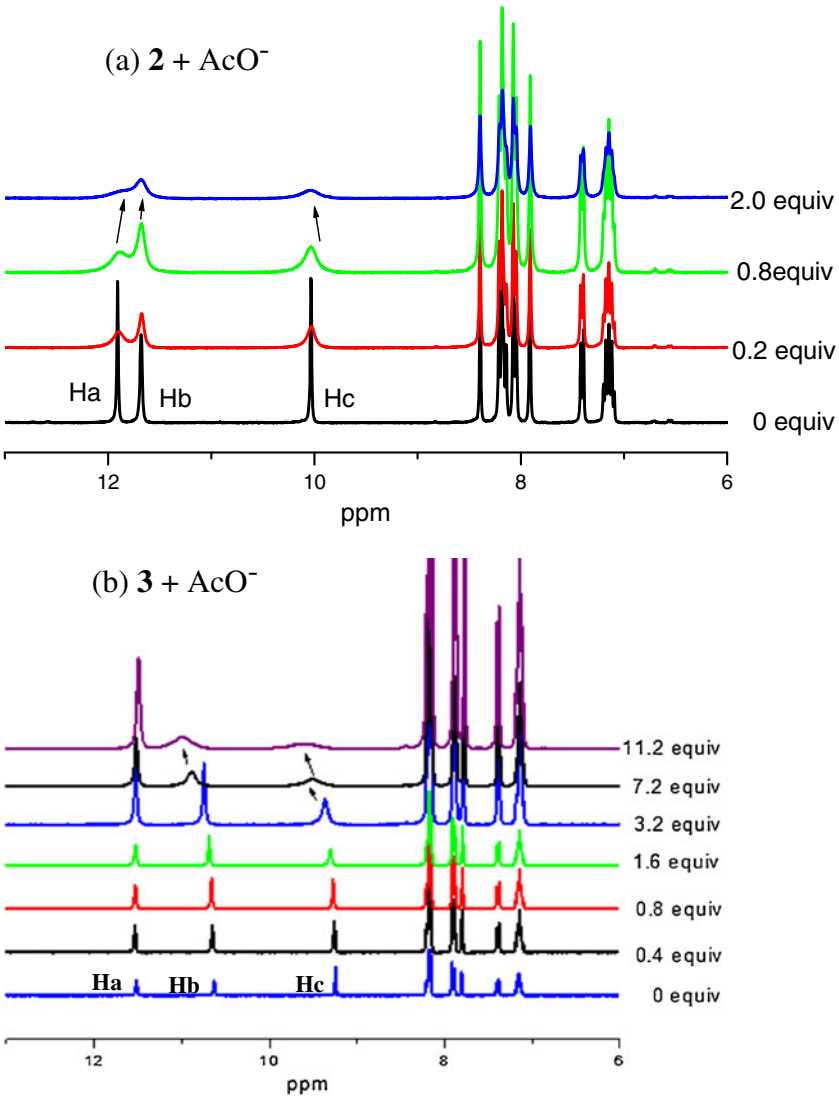
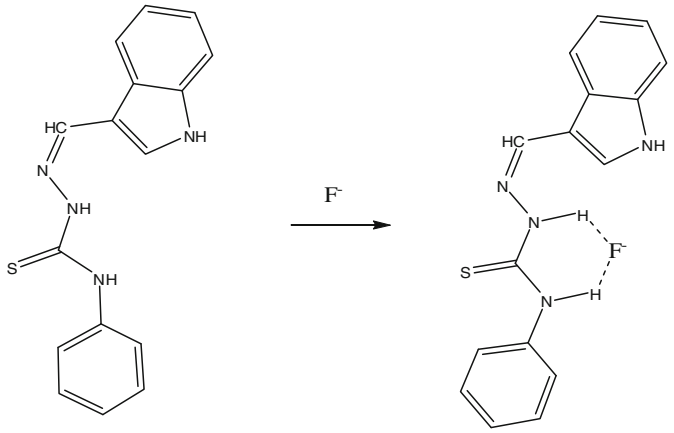


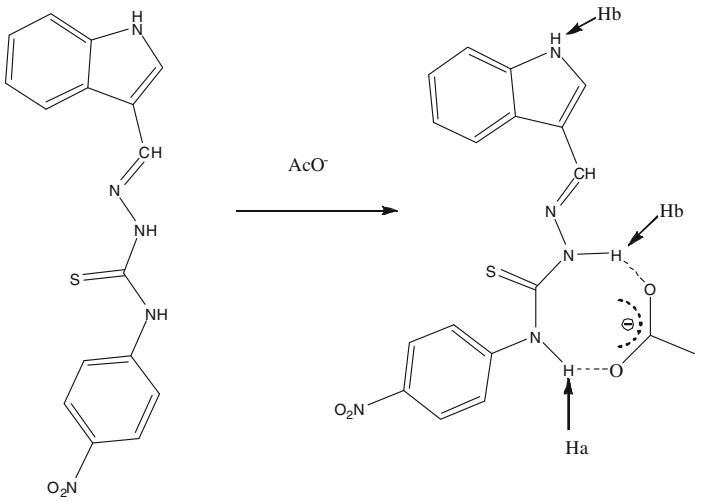
Fig. 7 ^1H NMR titration of receptor **2** and **3** (1.0×10^{-2} M) in DMSO-d_6 with $[Bu_4N]AcO$

Scheme 2 The proposed receptor-guest binding mode in solution

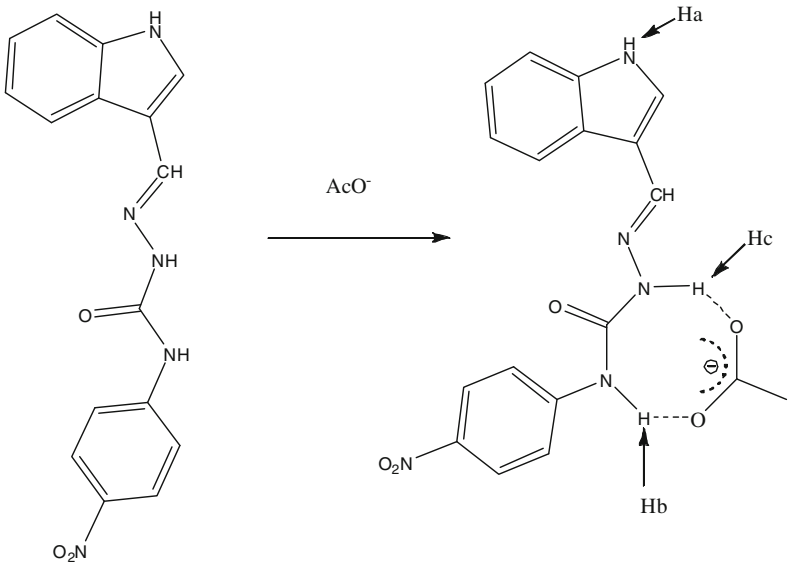
(a) **1** + F^-



(b) **2** + AcO^-



(c) **3** + AcO^-



correspondingly, and K_{ass} is the affinity constant of host-guest complexation [23].

$$X = X_0 + (X_{lim} - X_0) \left\{ C_H + C_G + 1/K_{ass} - \left[(C_H + C_G + 1/K_{ass})^2 - 4C_H C_G \right]^{1/2} \right\} / 2C_H \quad (1)$$

The Job's plot of receptor **2** and **3** with AcO^- are also 1:1. Affinity constants of the two receptors are also to be calculated this way.

These results are listed in the Table 1 below.

Single Crystal Structure Analysis

Yellow single crystals suitable for X-ray investigation were obtained by slow evaporation of the saturated receptor **3** DMF solution at room temperature. Unfortunately, we didn't get single crystal for other receptors explored.

The perspective view of receptor **3** with labeling scheme is given in Fig. 6. The complex consists of one receptor **3** and one solvent molecule DMF (See supporting information for detailed information). From Table 2, we can see all the three –NH of receptor **3** can form hydrogen bonds with another receptor **3** or DMF. But ^{1}H NMR titrations proved that only the –NH of (thio)urea participates in the recognition. We think the reason is that the distance of the three –NH in DMF solution is longer than in single crystal, so not all of them form the hydrogen bonding.

^{1}H NMR Titrations

A further study of the binding character of receptor-guest interactions was carried out through ^{1}H NMR titrations in DMSO-d_6

For receptor **1**, because the changes of the proton signals are very small in the presence of F^-, a good ^{1}H NMR titrations figure can not be obtained.

For receptor **2**, in the absence of the acetate anion (see Fig. 7), the proton signals at 11.92 ppm, 11.68 ppm and 10.04 ppm are assigned to Ha, Hb and Hc (marked in Scheme 2). When 0.2 equiv. of acetate were added in the solution of **2**, the signals of Ha and Hc broadened and the signals of Hb shifted slightly. Consequently, we thought Hb belonged to the –NH of indole which did not participate directly in the recognition. Upon addition of 2.0 equiv. of acetate,the signals of Ha and Hc downshifted, but not completely disappear. These results indicate that a hydrogen-bonding complex is formed between receptor **2** and acetate.

The receptor **3** acts similarly to receptor **2** in the process.

According to the Job's plot and ^{1}H NMR titrations, the proposed modes of host-guest bonding are depicted in Scheme 2.

Conclusions

In summary, we have developed three selective anion receptors **1**, **2** and **3** containing the (thio)urea binding sites, which easily form a stable 1:1 complex with anions. Receptor **1** exhibits the selective recognition capability towards F^- only. Receptor **2** and **3** provide improved anion binding sites, leading to higher binding affinity and especially to acetate. Furthermore, the color change of receptor **2** and receptor **3** upon addition of anions made the detection by 'naked-eye' possible.

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