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ORIGINAL ARTICLE

Study on the selectivity of anion receptors by adjusting the distance of two urea fragments and their analytical application

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Abstract Three anion receptors based on urea: **1** N, N′-bis-(p-nitrophenylaminocarbonyl)-Hydrazine, **2** N, N′-bis-(p-nitrophenylaminocar-bonyl)-ethylenediamine and **3** N, N′-bis-(p-nitrophenylaminocarbonyl)-1, 3-propane-diamine are designed and synthesized. Studies of UV–vis spectra presented that **1** was an excellent sensor of F^- and **2** was sensitive to $H_2PO_4^-$. Unfortunately, **3** can not distinguish the anions investigated in this paper. The color changes of the hosts upon the addition of a variety of structurally different anions were also utilized as naked-eye detection which is very convenient. It also revealed significantly that the distance between two recognition sites of receptor had an immediate effect on the selectivity of receptor for anions, which had been confirmed by the ^1H NMR titration and IR.

Keywords Anion recognition · Sensor · Selectivity

Introduction

For years, the recognition of inorganic and biotic anions has been a key research area of supramolecular chemistry [1]. Selectivity of anion recognition receptor is governed by the principle of size and shape complementarity: given a particular guest, a host must be designed whose steric configuration is complementary to that of the guest [2]. So the length of the binding sites defines the shape and the size of the anion, which is selective towards the anion. Creating selectivity that extends beyond the mere binding capacity and also allows anion recognition is the ultimate goal. However, this is also the true challenge in host design. As a corollary, selectivity could serve as a yardstick to asses the quality of a particular design attempt and document the progress [3, 4].

Inorganic anions are ubiquitous throughout biological system; it is believed that they carry genetic information (DNA is a polyanion) and participate in 70% of all enzymatic reaction. Among a range of biologically important anions, fluoride is of particular interest owing to its important role in the human body [5, 6]. Further more, phosphate esters exist commonly in nature in the form of nucleoside phosphates as components of RNA (or DNA) [7]. Thus, development of artificial fluoride receptors and phosphates receptors would afford new methodologies for detection, separation, or transport of biologically important fluoride anion and phosphate anion. Many anion receptors based on urea emerged after the original papers by Wilcox [8] and Hamilton [9] on urea–anion interactions. Noticeably, a series of receptors based on urea exhibit prominent selectivity [10]. A lot of examples have been reported of anion receptor systems that urea and urea groups [1] to complex anionic guests. In this paper, three receptors bearing two urea groups as colorimetric group were designed and synthesized. The steric configuration can be adjusted to an anion's bulk by changing the distance between the two fragments and receptors **1** and **2** have potential application in analytical inorganic anions by naked-eye detection.

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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.

General method

^{1}H NMR spectra were recorded on a Varian UNITY Plus-400 MHz Spectrometer at the Key Laboratory of Functional Polymer Materials of Ministry of Education, Nankai University. UV–vis Spectroscopy titrations were performed on a Shimadzu UV2450 Spectrophotometer at 298 K. Infrared spectra were measured on a Perkin Elmer Model 1600 FT-IR Spectrophotometer. Elemental analysis for C, H, and N were carried out on a PerkinElmer 240C element analyzer at the Institute of Elemento-Organic Chemistry, Nankai University.

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

Synthesis of receptors

1, **2** and **3** were synthesized according to the route shown in Scheme 1 and 1-isocyanato-4-nitrobenzene was acquired by the reported process [11]. 1-isocyanato-4-nitrobenzene (15 mmol, 2.46 g) was dissolved in acetonitrile (50 ml). To a solution of 0.0075 mol of hydrazine, ethylenediamine and 1, 3-propylenediamine was added respectively. The mixture was refluxed on a water bath for 3 h. The solid product, obtained on cooling, was washed with distilled water and recrystallized from ethanol. For **1**, yield 73%, ^{1}H NMR (400 MHz; DMSO-d_6; Me_4Si) 7.8 (4H, d, Ph), 8.2 (4H, d, Ph), 8.4 (2H, s, CONHNH), 9.6 (2H, d, PhNHCO), Elemental analysis: Calc. for $C_{14}H_{12}N_6O_6$: C, 46.67; H, 3.36; N, 23.33; Found: C, 46.70; H, 3.61; N, 23.13. For **2**, yield 68%,^{1}H NMR (400 MHz DMSO-d_6; Me_4Si) 1.7–1.9 (4H, m, NCH_2), 6.5 (2H, s, CONH), 7.6 (4H, d, Ph), 8.1 (4H, d, Ph), 9.4 (2H, s, PhNHCO); Elemental analysis: Calc. for $C_{16}H_{16}N_6O_6$: C, 49.49; H, 4.15; N, 21.64; Found: C, 49.40; H, 4.41; N, 22.13. For **3**, yield 67%, ^{1}H NMR (400 MHz DMSO-d_6; Me_4Si) 1.6–1.9 (2H, m, CH_2), 1.9 (s, NCH_2), 6.4–6.6 (2H, m, CONH), 7.6 (4H, d, Ph), 8.1 (4H, d, Ph), 9.3 (2H, s, PhNHCO); Elemental analysis: Calc. for $C_{17}H_{18}N_6O_6$: C, 50.75; H, 4.51; N, 20.89; Found: C, 51.08; H, 4.26; N, 21.05.

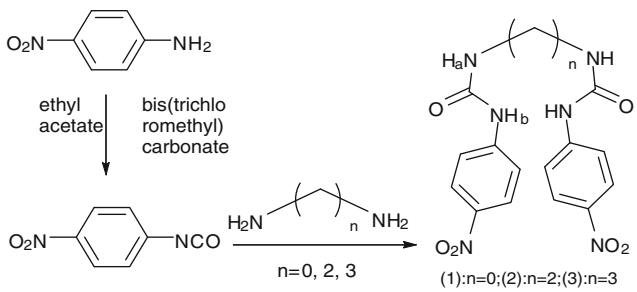
Results and discussion

UV–vis anion titration studies

In order to study the binding selectivity of receptor **1**, **2** and **3**, UV–vis titrations were carried out in DMSO at a concentration of 1.0×10^{-5} M by adding tetrabutylammonium salts of anions at 298.2 ± 0.1 K. Among the six anions investigated in DMSO solution, namely, AcO^-, F^-, $H_2PO_4^-$, Cl^-, Br^- and I^-, **1** exhibited selective recognition for F^- and **2** for $H_2PO_4^-$ as shown in Fig. 1.

Figure 1 (a) shows the UV–vis spectral changes of **1** during the titration with fluoride ions and Fig. 1 (b) shows the UV–vis spectral changes of **2** during the titration with dihydrogen phosphate ions. It turns out that the UV–vis absorption band of **1** and **2** in DMSO undergoes a red shift. In the absence of anions, the absorption spectrum of **1** is characterized by the presence of one absorption maximum peak at 345 nm. Upon addition of F^-, the absorption peak 345 nm decreases while a new peak forms at 354 nm. On the other hand, the absorption peaks at 350 nm of **2** was shifted to 367 nm upon $H_2PO_4^-$ titration. In addition, the presence of well-defined isosbestic points at 350 nm for (a) and 354 nm for (b) indicated that there form the stable complex with a certain stoichiometric ratio between the receptors and anions [12]. However, as the Cl^-, Br^- and I^- were titrated into **1**, **2** and **3**, the spectra displayed slightly change even the anions were excessive. In comparison, receptor **3** does not distinguish AcO^-, F^- and $H_2PO_4^-$ obviously.

In Fig. 2, job's plot [13] of receptor **1** and F^- in DMSO shows the maximum at a molar fraction of 0.5. This result indicates that the receptor **1** binds fluoride anion guest with a 1:1 ratio. Moreover, similar results can also be obtained for other anions (AcO^- and $H_2PO_4^-$). The semblable job's plot can be acquired from receptor **2** and **3**.



Scheme 1 The synthesis of receptors

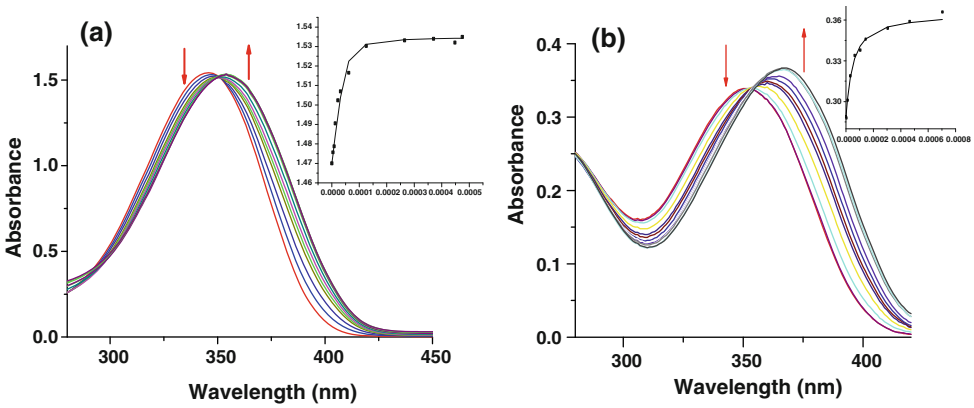


Fig. 1 **a** Family of spectra taken in the course of the titration of a 5.0×10^{-5} M solution of **1** with a standard solution of F^- at 298.2 ± 0.1 K. **b** Family of spectra taken in the course of the titration of a 1.0×10^{-5} M solution of **2** with a standard solution of $H_2PO_4^-$

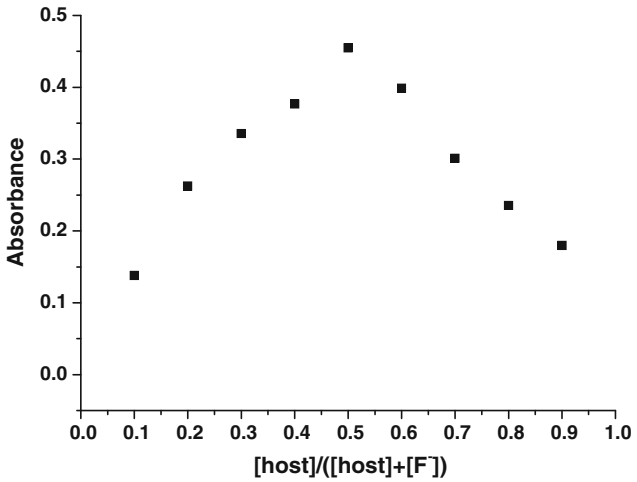


Fig. 2 Job's plot for complexion of receptor **1** with F^- determined by UV–vis in DMSO at 298.2 ± 0.1 K, [**1**] + [F^-] = 3.5×10^{-5} M

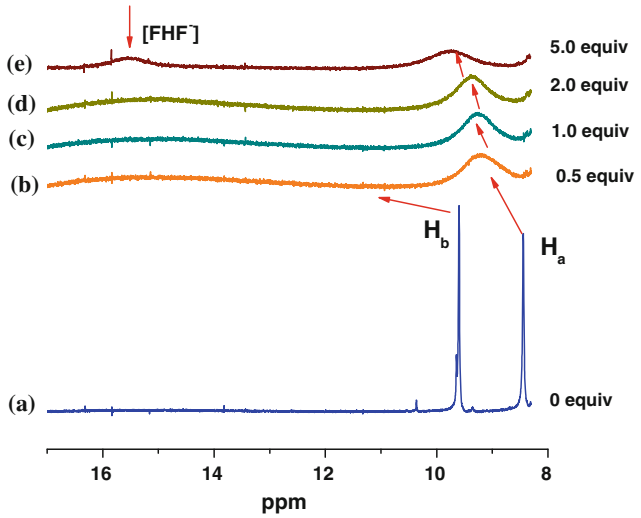


Fig. 3 ^{1}H NMR spectra of **1** in DMSO-d_6 **a** the absence and the presence of **b** 0.5, **c** 1.0, **d** 2.0, **e** 3.0, **f** 5.0 equiv of F^-

Table 1 The affinity constants of receptor **1**, **2** and **3** with anions at 298.2 ± 0.1 K, respectively

Anions	F^-	$H_2PO_4^-$	AcO^-	Cl^-	Br^-	I^-
log $K_{S,1}$	5.31 ± 0.35	3.66 ± 0.14	3.47 ± 0.18	ND	ND	ND
log $K_{S,2}$	3.21 ± 0.18	4.35 ± 0.23	3.50 ± 0.22	ND	ND	ND
log $K_{S,3}$	3.49 ± 0.19	3.78 ± 0.21	3.49 ± 0.21	ND	ND	ND

ND indicated that the spectra showed little or no change with the addition of the anion so that the affinity constant can not be determined using the spectra

Affinity constants of receptor **1**, **2** and **3** for anionic species are calculated and listed in the Table 1 below.

Compared with the previous research in previous research [14], receptor **1** and receptor **2** has higher selectivity than compound **2** and **4**. The reason may be that the steric configuration of receptor **1** is proper to F^-. Spherical anions can geometrically match the receptor better than trigonal, linear, and tetrahedral anions. Further more, the radius of F^- is suitable for receptor **1**. Receptor **2** is sensitive to $H_2PO_4^-$, which is also due to the steric configuration-matching. For receptor **3**, C_3 chain makes the two urea fragments too far to have selectivity to the guest we investigated.

1H NMR anion titration studies

To further look into the nature of host–guest interactions, ^{1}H NMR titration experiments were conducted in DMSO-d_6.

Figure 3 presents the ^{1}H NMR spectra changes of the –NH moiety assigned as H_a and H_b (marked in Scheme 1) upon addition of F^-. It is obvious that upon addition of 0.5 equiv F^- ions, H_a broadened, upfield shifted, and H_b disappeared, which implied interaction of the fluoride ion with H_a via favourable hydrogen bonding and deprotonation of H_b [14–17]. In this ^{1}HNMR titration experiments, we can see complete deprotonation is not achieved until an excess of the anion is added, presumably due to receptor **1** being

more acidic than previous studies [14], which made the H_b more active, and deprotonation achieved when 0.5 equiv F^- ions is added. Other studies in our group have similar experimental phenomena [16, 17].

At the same time a new signal at 15.8 ppm appears clearly, which is ascribed to the FHF^- dimer [18, 19]. The new peak at 15.8 ppm indicates the deprotonation of H_b. In the other hand, the signals (shown in Fig. 4) of H at phenyl ring fragment have upfield shifted, which means that electron density in the phenyl fragment was increased because of deprotonation of H_b [16]. These spectra changes can prove ulteriorly that the complex between receptor **1** and F^- has formed. In addition, we show the stepwise changes [20] for **1** and F^- interaction.

The interaction of receptor **2** and $H_2PO_4^-$ exhibits another way of combination (Fig. 5). In all cases the addition of $H_2PO_4^-$ produced downfield shift of the respective urea protons [14]. This suggests the complex between receptor **2** and $H_2PO_4^-$ being formed. Remarkably, the water peak also downfield perturbations and grows bigger gradually as the increasing quantity of $H_2PO_4^-$, which owe to the proton transferring from $H_2PO_4^-$ to H_2O.

Infrared spectral analysis of anion addition

Infrared spectra of receptor 1 in DMSO and the receptor 1 with F^- are presented in Fig. 6. The main characteristic peak of recognition sites of 1 is N–H flexible vibration signal occurred at 3471.03 cm^{-1}. After 3 equiv of F^- addition, the flexible vibration peak of N–H was moved to 3463.35 cm^{-1}. Further more, the peak grows broader. These changes are caused by the N–H···F hydrogen bonding formed between the receptor and F^-.

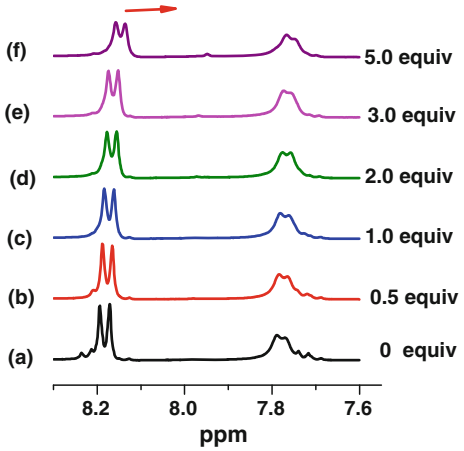


Fig. 4 Phenyl ring fragment ^1H NMR spectra of **1** in DMSO-d_6 **a** the absence and the presence of **b** 0.5, **c** 1.0, **d** 2.0, **e** 3.0, **f** 5.0 equiv of F^-

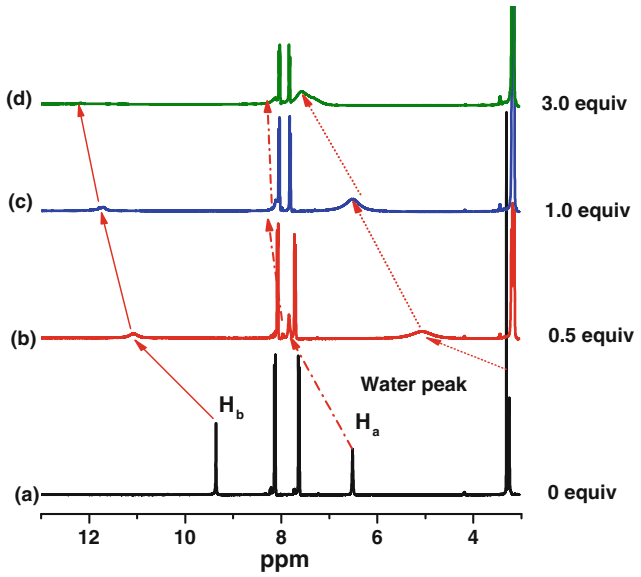


Fig. 5 The partial ^1H NMR spectra of **2** in DMSO-d_6 **a** the absence and the presence of **b** 0.5, **c** 1.0, **d** 3.0 equiv of $H_2PO_4^-$

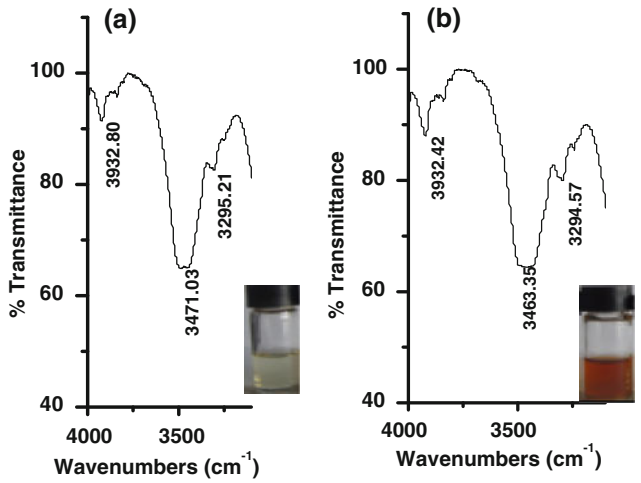


Fig. 6 N–H infrared spectra of **1** in DMSO-d_6, **a** the absence and the presence of **b** 3.0 equiv of F^-

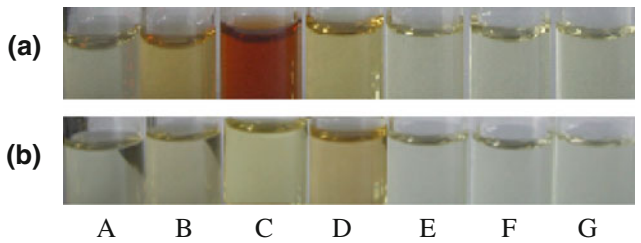


Fig. 7 Color changes of receptors **1** (**a**) and **2** (**b**) in DMSO. [**1**] = [**2**] = 1.0×10^{-5} M, [anion] = 3 equiv: *A* free receptor, *B* AcO^-, *C* F^-, *D* $H_2PO_4^-$, *E* Cl^-, *F* Br^- and *G* I^-

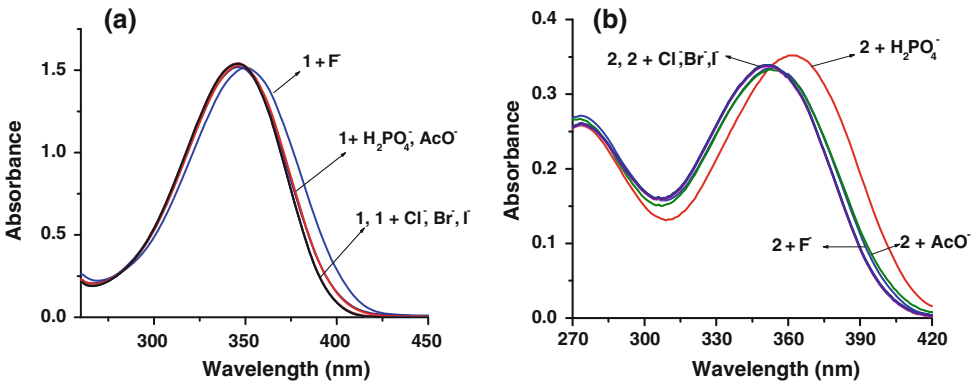


Fig. 8 **a** UV–vis changes of **1** operated in DMSO (5.0×10^{-5} M) after the addition of **1** equiv of anions. **b** UV–vis changes of **2** operated in DMSO (1.0×10^{-5} M) after the addition of **3** equiv of anions

Analytical applications

According to the results summarized in Table 1 of analyses performed by UV–vis titration using the method of non-linear least square fitting, the anion affinity constants of receptor **1** are in the order: $F^- > H_2PO_4^- > AcO^- >> Cl^-$, Br^- and I^-, while that of receptor **2** are in the order: $H_2PO_4^- > AcO^- > F^- >> Cl^-$, Br^- and I^-, which implied that receptor **1** and **2** could have potential application in analytical chemistry. To prove the supposition, color changes of receptor **1** and **2** were tested in DMSO (1.0×10^{-5} M). Upon addition of 3 equiv anions, the color of solution of receptor **1** changed from light yellow to red by the introduction of F^- while the color changed to light red for receptor **2** by $H_2PO_4^-$ (shown in the Fig. 7).

A further investigation were performed to confirm the results by UV–vis changes of receptor **1** and **2** in DMSO after the addition of 1 equiv anions, namely, AcO^-, F^-, $H_2PO_4^-$, Cl^-, Br^- and I^-. **1** exhibited selective recognition for F^- and **2** for $H_2PO_4^-$ as shown in Fig. 8, respectively.

Furthermore, the processes of recognition were accompanied by distinct color changes. Thus, the receptor **1** could be considered as a potential F^- anion detector and the receptor **2** for $H_2PO_4^-$.

Conclusions

In summary, a series of new receptors have been prepared and characterized. UV–vis spectral titration experiments revealed all receptors form 1:1 stoichiometric complexes with anions in DMSO solution, especially, **1** has a high selectivity for F^- and **2** is a good sensor for $H_2PO_4^-$. Moreover, the nature of binding model of receptor **1** with F^- and receptor **2** with $H_2PO_4^-$ were investigated by proton NMR anion titration. Hence, by changing the distance between the two urea fragments, receptors will exhibit different selectivity towards anions which have different size and shape. Also, this could provide a convenience and shortcut method as an application of analytical chemistry.

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