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ORIGINAL PAPER

Efficient fluoride-selective receptor: experiment and theory

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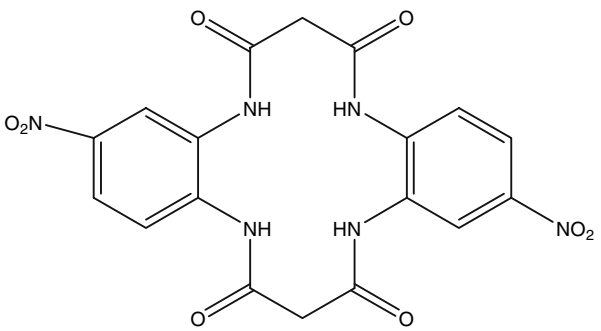
Abstract A novel artificial receptor, (3′-nitrobenzo)[2,3-d]-(3″-nitrobenzo)[9,10-d]-1,4,8,11-tetraazacyclotetradecane-5,7,12,14-tetraone, has been synthesized and shows high selective and recognitive ability for F^- among F^-, Cl^-, Br^-, AcO^-, $H_2PO_4^-$ by UV-vis and ^1H NMR titration experiments. Theoretical investigations suggest that the fluoride selectivity among various anions comes from the fact that the fluoride approaches much closer to the amide protons than other anions located above the cavity. The interaction energies support the large binding ability difference between F^- and $Cl^-/Br^-/AcO^-/H_2PO_4^-$.

Keywords Anion recognition · Amido · Macrocyclic compound

Introduction

Because anions play significant roles in life processes and in the environment, the development of new anion receptors is of great interest and significance in host-guest chemistry [1]. Study of anion receptors has special potential applications in the synthesis of anion sensors [2], membrane transmit carrier [3] and mimic enzyme catalyst synthesis, etc. [4, 5] Also their effects as environmental pollutants have only recently been realized and several types of synthetic chemosensors have been developed to date. For the molecular designs of the chemosensors, how to achieve the specific recognition of a certain anion and how to convert the recognition event into a signal are the key points [6].

Among various important anionic analytes, biologically important fluoride anion is one of the most significant due to its role in dental care and treatment of osteoporosis. As the smallest and the most electronegative atom, fluoride has unique chemical properties and can form the strongest hydrogen-bond interaction with hydrogen-bond donors. Many examples are available on selective macrocyclic amide receptor molecules for fluoride anion. [7–9] However, there is paucity of reports that describe the change in color in the visible region of the spectrum and thereby allow the naked eye detection for fluoride anion. With this information, we designed and synthesized a new receptor **1** (Scheme 1) containing tetraamide



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Scheme 1 The structure of receptor **1**

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macrocyclic moiety and nitryl was made as the colorimetric group, in order to achieve a higher affinity constant for fluoride anion. And its anion binding properties were investigated by UV-vis, ^{1}H NMR titration experiments and theoretical investigations. Experimental and theoretical results show that receptor **1** has high sensitivity and selectivity only to F^- among F^-, Cl^-, Br^-, AcO^-, $H_2PO_4^-$, and can thus be used as a convenient detector for fluoride anion.

Results and discussion

Titration experiments for anion recognition of **1** were performed by UV-vis spectroscopy in DMSO.

As shown in (a) of Fig. 1, the receptor has certain absorption band centered at 312 nm, and the intensity of absorbance at 312 nm decreases when fluoride anion is added. At the same time, a new absorbance peak at 450 nm develops, and the intensity of this absorbance increases. The color of the solution changed from yellowish to yellow gradually as the concentration of fluoride anion increased (Fig. 2). In addition, there appears one clear isosbestic point at 375 nm. This indicates that there forms the stable complex with a certain stoichiometric ratio between the receptor **1** and fluoride anion. The addition of AcO^- leads to similar spectral changes (Fig. 1), but the additions of $H_2PO_4^-$, Cl^- show small spectral changes and the addition of Br^- virtually leads to no spectral changes.

Job plot for receptor **1** at 298 K with F^- as a guest in DMSO solution showed the maxima at a mole fraction of 0.5, which signified that the host bound the anionic guest in a 1:1 ratio. Affinity constants of receptor **1** for anionic species are calculated according to the eq. 1, 1:1 host-guest complexation [10–13].

$$X = X_0 + 0.5\Delta\varepsilon\{c_H + c_G + 1/K_s - [(c_H + c_G + 1/K_s)^2 - 4c_Hc_G]^{1/2}\} \quad (1)$$

Where, c_G and c_H are the concentration of guest and host, respectively. X is the intensity of absorbance at certain concentration of host and guest. X_0 is the intensity of absorbance of host when the anion isn't added. K_s is the affinity constant of host-guest complexation. $\Delta\varepsilon$ is the change in molar extinction coefficient. The fitting curves for affinity constants are shown in Fig. 3. The affinity constants obtained using the method of non-linear least square calculation are summarized in Table 1.

As can be seen in Table 1, the anion affinity abilities of receptor **1** are in the order of $F^- > AcO^- > H_2PO_4^-$ ~

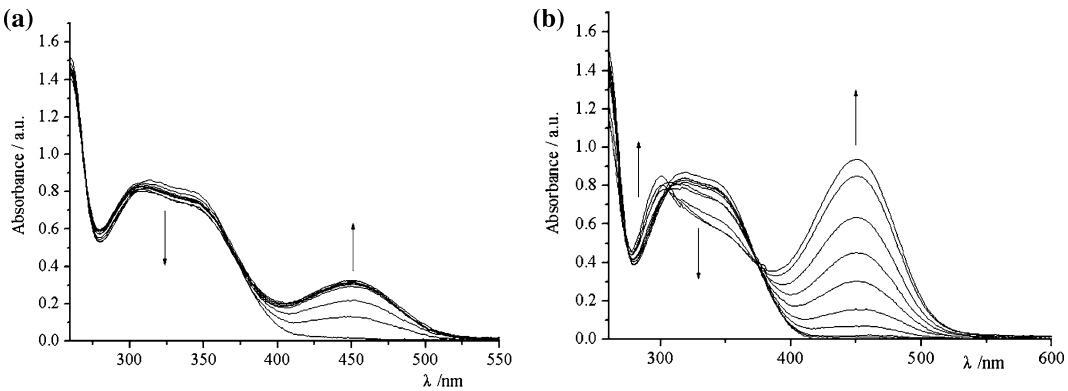


Fig. 1 UV-vis spectral changes of receptor **1** upon the addition of various anions (**a**) F^-, (**b**) AcO^- [**1**] = 5.0×10^{-5} mol/l [anion] = 0–180×10^{-5} mol/L. Arrows indicate the direction of increasing anion concentration

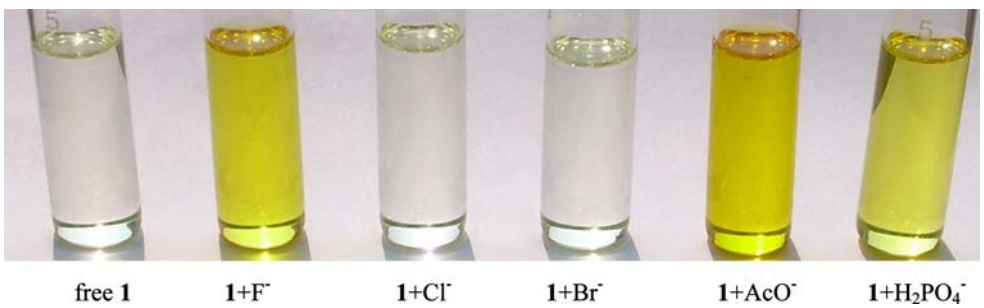


Fig. 2 Color changes seen for DMSO solution of receptor **1** upon the addition of anions as TBA salts. [**1**] = 5×10^{-4} mol/l [anion] = 1×10^{-3} mol/l

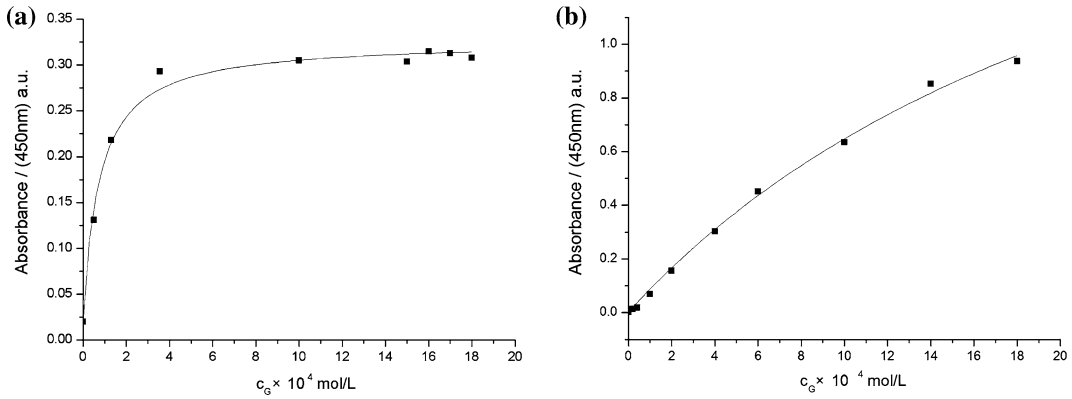


Fig. 3 The fitting curve for various anions (**a**) F^-, (**b**) AcO^-

Table 1 Affinity constants of receptor **1** with various anions

Anion	K_s (M^{-1})
F^-	$(1.34 \pm 0.1) \times 10^4$
AcO^-	368 ± 54
$H_2PO_4^-$	<10
Cl^-	<10
Br^-	ND

ND = not determined

$Cl^- > Br^-$. The affinity constant for F^- is almost 36-fold greater than that for AcO^-, almost 1000-fold greater than that for $H_2PO_4^-$, Cl^-. The receptor almost had no binding abilities to Br^-. Figure 1 shows the spectrum of acetate is more remarkable than fluoride, but the affinity constant value is not dependent on spectral response and is dependent on the concentration of anion when the interactions get to equilibrium. When the interactions get to equilibrium, the concentration of fluoride is smaller than acetate. This indicates the affinity constant of acetate is smaller than that of fluoride, fitting curves also prove this (Fig. 3). In addition, the affinity constant value is not dependent on the color change of reaction solution, and the color change of reaction solution indicates the change of energy order before and after reaction of receptor with anion. This suggests that the apparent color changes are noted not only fluoride, acetate, but also hydrogen phosphate in Fig. 2, but the latter affinity constant is too small.

Very recently, a number of fluorogenic and/or chromogenic anion sensors comprising recognition moieties with acidic protons such as urea, thiourea, or amide have been reported to undergo an anion-induced deprotonation [14–16]. According to these reports, there appeared one new triplet resonance at about 16.1 ppm, the characteristic resonance of bifluoride (F-H-F), or the protons of non-interaction sites exhibited significant changes in chemical shifts. In general, the formation of hydrogen bonding causes the

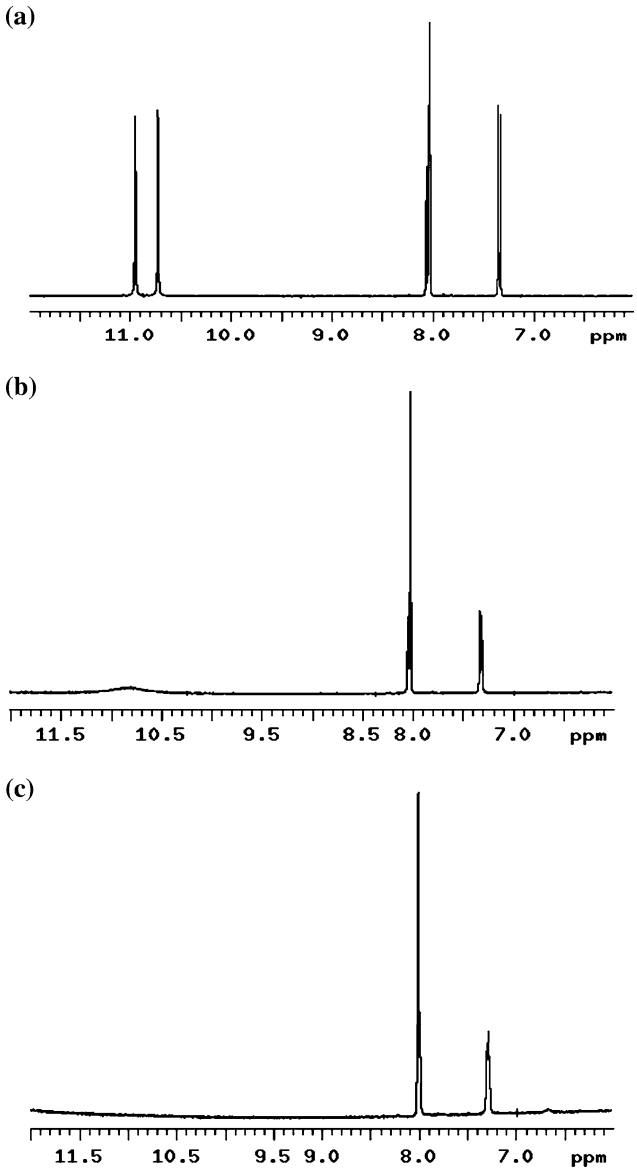


Fig. 4 Partial ^1H NMR (400 MHz) spectra of receptor in DMSO-d_6 at 298 K in (**a**) the absence, (**b**) the presence of 1 equiv. and, (**c**) the presence of 5 equiv. of $[(n\text{-Bu})_4N]F$

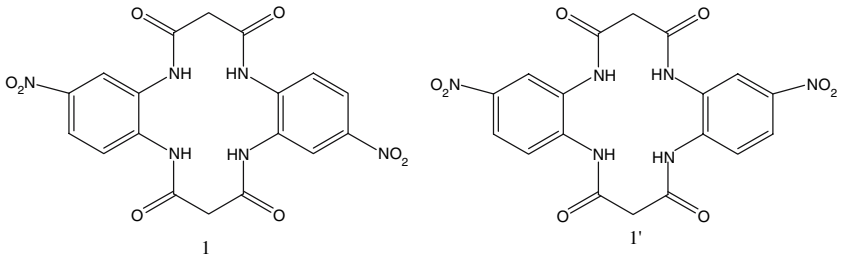
down field shift of interacted proton, however, there also exist the disappearance of interacted proton [17]. To look into the binding ability of receptor **1** for F^-, ^1H NMR titration experiments are performed in DMSO-d_6. A partial ^1H NMR spectrum of receptor **1** is shown in Fig. 4. In this paper, there does not appear one new triplet resonance at about 16.1 ppm and the chemical shift of phenyl proton signals almost lead to no changes. In addition, the signals for the amide –NH protons (δ10.96, δ10.74) broaden gradually at 10.85 ppm when the addition is 1 equiv. of [(n-Bu)$_4$N]F and disappear completely when the addition is 5 equiv. of [(n-Bu)$_4$N]F. Due to the affinity constant between receptor **1** and fluoride is not very big (1.34×10^4 see Table 1), receptor **1** could not combine fully with fluoride anion when the addition is 1 equiv. of [(n-Bu)$_4$N]F. Combined fluoride anion forms hydrogen bonding with receptor **1** which causes the NH protons downfield. Non-combined fluoride anion exists the ambience of receptor **1** and forms shield effect that induces the NH protons upfield. The above two factors result in the signals of NH protons broaden gradually and disappear completely. The results probably indicate that receptor **1** does form hydrogen bonds between the amide protons and fluoride.

Obviously, the recognition function of **1** for fluoride anion is the most remarkable one. The reason may be that (1) for the cavity in receptor **1** spherical anions matches the receptor in space better than trigonal, tetrahedral anions. (2) Recently, Kim et al. [18] have reported results of ab initio calculations for cyclic tetra- and hexapeptides and their anion complexes. They reported that the F^- anion was indeed well fitted for the 18-membered hexapeptide ring and was located inside the cavity and bound by all six amide hydrogen atoms. Comparatively, the receptor **1** we synthesized here is a 14-membered macrocycle and the cavity is smaller for fitting F^- anion inside. And the anions (F^-, Cl^-, Br^-, AcO^-, $H_2PO_4^-$) may be positioned above the 14-membered macrocycle of receptor **1** and bound by all four amide hydrogen atoms according to theoretical investigations (detailed in the following text). This high selectivity is ascribed to a decrease in the binding ability between the amide-based receptor and other anions (AcO^-, $H_2PO_4^-$, Cl^-, Br^-), only F^-, an anion expected to form strong hydrogen bonds, could form stable binding complex with receptor. This suggests that the spacer units are responsible for anion-selectivity. These results provide useful experimental basis for the design of fluoride anion recognition's sensor.

Theoretical investigations on the structure

We obtained the double-nitration product, which exists as two isomers (trans- (**1**) and cis-(**1′**) shown in Scheme 2). We tried to synthesize each isomer and the crystal. Unfortunately, we could not obtain the crystal up to date and could not confirm that the product is isomer **1** or **1′** by ^1H NMR, IR and elemental analysis, since the two isomers have the same element percentage and the difference of ^1H NMR and IR spectrum is very small. Therefore, we optimized the geometries of the two isomers (Fig. 5) and theoretical investigations were undertaken in an attempt to further rationalise the novel anion selectivity trends using Density functional theory at B3LYP/3-21G level with Gaussion03 program [19]. The calculation results on total energy and the energy gap of E_{LUMO}, E_{HOMO} of the two isomers are listed in Table 2.

Scheme 2 The structure of **1**(trans-) and **1′**(cis-) compound



From Table 2, one can see that the total energy of isomer **1** is lower than that of **1′** by 21.49 kJ/mol. This indicates that isomer **1** is more stable than **1′** thermodynamically. On the other hand, the energy gap ΔE (E_{LUMO}–E_{HOMO}) of isomer **1** is larger than that of isomer **1′**. This result implied that isomer **1** has lower reaction activity than isomer **1′**. Thus isomer **1** is more easily obtained during the synthesis. Therefore, we conclude that the product we obtained may be isomer **1**(trans-) and the structure of reported compound has certain reliability according to the data of ^1H NMR, elemental analysis, FAB-MS and theoretical investigations. In addition, if this compound is the mixture of cis/trans isomers a proper HPLC system cannot

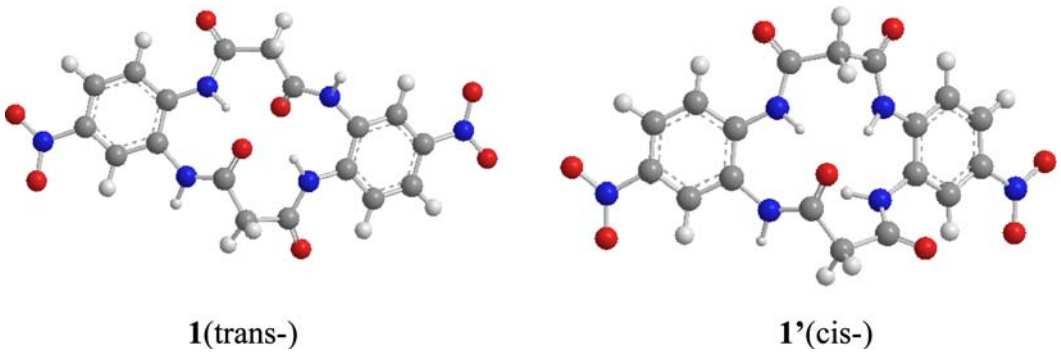


Fig. 5 Optimized configuration of isomer **1**(trans-) and **1′**(cis-)

Table 2 The total energy (E_T) and energy gap of $\Delta E(E_{LUMO}–E_{HOMO})$ of **1** and **1′** obtained at B3LYP/3-21G level

Compound	**1**	**1′**
E_T (a.u.)	–1615.5295	–1615.5214
$E_{relative}$(kJ/mol)	0	21.49
E_{LUMO} (a.u.)	–0.10455	–0.11335
E_{HOMO} (a.u.)	–0.24838	–0.25342
ΔE (kJ/mol)	377.63	367.75

1 a.u. = 2625.5 kJ/mol

confirm which is cis, which is trans, because these cis/trans isomers are new compounds.

The B3LYP/3-21G-optimized structures for the complexes of receptor **1** with various anions (F^-, AcO^-, $H_2PO_4^-$, Cl^-, Br^-) [20] are represented in Fig. 6. The interaction energies without basis set superposition error correction are –829.44, –292.00, –293.93, –396.43, –379.03 kJ/mol for F^-, Cl^-, Br^-, AcO^-, and $H_2PO_4^-$, respectively.

The large binding energy difference between F^- and $Cl^-/Br^-/AcO^-/H_2PO_4^-$ may result in the binding selectivity for F^- over $Cl^-/Br^-/AcO^-/H_2PO_4^-$, as is observed in the UV-vis titration experiment. The binding energy comes from the strongly charged hydrogen bonding between anion and four amide protons. The interatomic distances between anion and four amide protons are 1.578, 1.595, 1.578, and 1.595 Å for fluoride, 2.251, 2.219, 2.251, 2.219 Å for chloride, and 2.349, 2.346, 2.349, 2.346 Å for bromide. As for acetate, two oxygens participated in the formation of hydrogen bond. The interatomic distances between acetate oxygen atoms and four amide protons are 1.779, 1.866 Å and 1.775, 1.906 Å. However, only one oxygen atom formed hydrogen bond with three amide protons as shown in Fig. 6. The interatomic distances between dihydrogen phosphate oxygen atoms and three amide protons are 1.561, 1.715 Å and 1.868 Å. The fluoride is smaller and harder than chloride, bromide, acetate, dihydrogen phosphate, and it can approach much

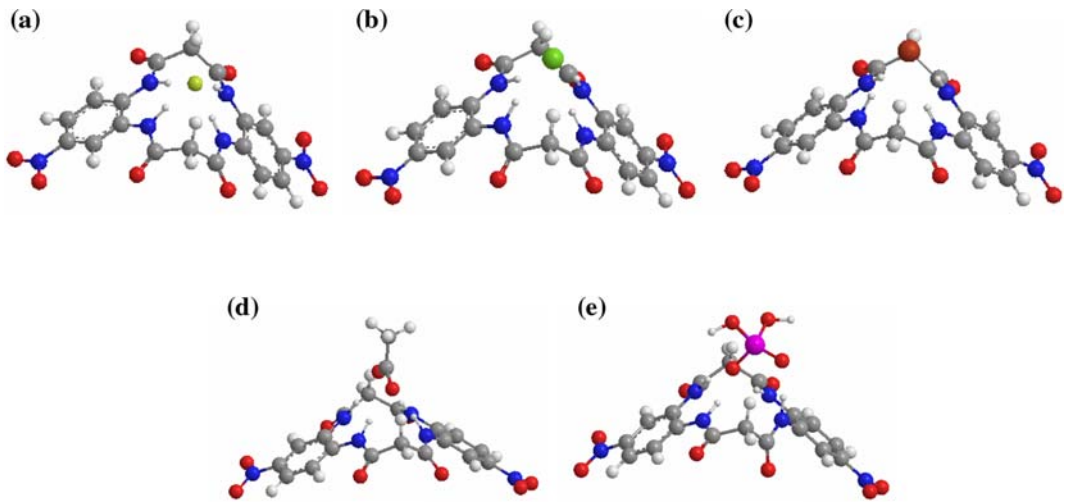


Fig. 6 B3LYP/3-21G-predicted optimized structures of complexes of **1** with fluoride (**a**), chloride (**b**), bromide (**c**), acetate (**d**), and dihydrogen phosphate (e)

closer toward the cavity. As is well known, the hydrogen bonding ability of fluoride atom is stronger than that of oxygen atom. Thus the affinity constant of fluoride anion is bigger than that of acetate anion. It is interesting to note that the interatomic distances for chloride and bromide are not so different; hence, the hydrogen bonding energies are predicted to be similar. As a matter of fact, the calculated interaction energies are almost equivalent for chloride and bromide. As for acetate and dihydrogen phosphate, the interatomic distances are not so different and the hydrogen bonding energies are predicted to be similar. However, the affinity constants of experimental results are different. That may be that two oxygen atoms participate in the formation of hydrogen bonding for acetate anion, while, there only one oxygen atom for dihydrogen phosphate. These studies on this problem are in progress.

Experimental section

Most of the starting materials were obtained commercially and all reagents and solvents used were of analytical grade. All anions, in the form of tetrabutylammonium salts, were purchased from Sigma-Aldrich Chemical Co., stored in a desiccator under vacuum containing self-indicating silica, and used without any further purification. Dimethyl sulfoxide (DMSO) was distilled in vacuo after dried with $CaSO_4$. Tetra-*n*-butylammonium salts (such as (n-$C_4H_9)_4NF$, (n-$C_4H_9)_4NCl$, (n-$C_4H_9)_4NBr$, (n-$C_4H_9)_4NAcO$, (n-$C_4H_9)_4NH_2PO_4$) were dried for 24 h in vacuum with P_2O_5 at 333 K before use. C, H, N elemental analyses were made on a Vanio-EL. ^1H NMR spectra were recorded on a Varian UNITY Plus-400 MHz Spectrometer. FAB-MS was made on VG ZAB-HS. UV-vis Spectroscopy titration were made on BECKMAN DU-8B Spectrophotometer at 298 K. The series of solutions of dimethyl sulfoxide having same concentration host and different concentrations of anions of tetra-n-butylammonium salts 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.

Receptor **1** was synthesized following the methodology shown in Scheme 3.

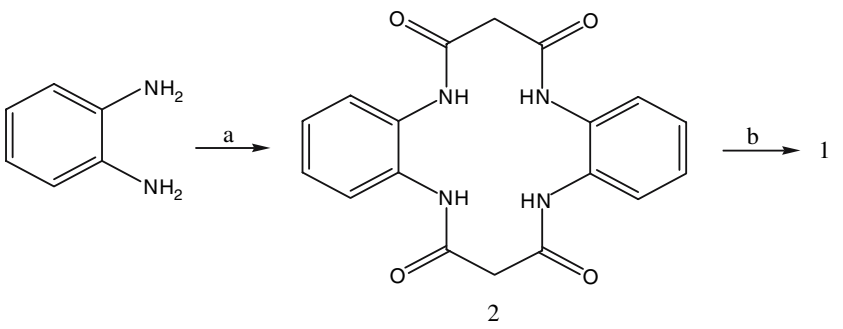
Bis-(benzo)-[2,3-d][9,10-d]-1,4,8,11-tetraazacyclotetradecane-5,7,12,14-tetraone(2)

(**2**) was synthesized according to reported process [21].

(3′-Nitrobenzo)[2,3-d]-(3″-nitrobenzo)[9,10-d]-1,4,8,11-tetraazacyclotetradecane-5,7,12,14-tetraone(1) Bis-(benzo)-[2,3-d][9,10-d]-1,4,8,11-tetraazacyclotetradecane-5,7,12,14-tetraone(10 mmol, 3.5 g) was dissolved in concentrated H_2SO_4 (43 ml). Fuming HNO_3 (2.1 ml) was added dropwise with stirring at 273 K. After the addition was completed, the mixture was stirred for 2 h and then poured into ca. 200 ml ice-water. The solution was filtered and gave a yellow solid, washed with distilled water, recrystallized from methanol and dried in vacuum. Yield 84.8%.^1H NMR(400 MHz DMSO-d_6) δ10.96 (s, 2H), 10.74 (s, 2H), 8.04, 7.3 (6H), 3.3 (s, 4H), Elemental analysis: Calc. for $C_{18}H_{14}N_6O_8$: C, 48.88; H, 3.19; N, 19.00; Found: C, 48.76; H 3.58; N, 18.51. FAB-MS(m/z): 443.1 $(M + 1H)^+$

Conclusion

In conclusion, we have succeeded in preparing anion sensors that allow for the facile colorimetric detection of fluoride anion. It has been shown that receptor **1** has good selective recognition for fluoride anion over other anions examined. However, the selectivity between F^- and AcO^- is not sufficient for future applications. The selectivity is probably influenced by size complementarity between anions and cavity. According to Kim's calculation, F^- anion was well fitted for the 18-membered hexapeptide ring. Thus we can



Scheme 3 Reagents and conditions:
(**a**) $CH_2(COOC_2H_5)_2$, pyridine, reflux 72 h at N_2
(**b**) concentrated H_2SO_4, fuming HNO_3, 273 K

modify the receptor by tuning the size of macrocycle, receptor **1** (for example 16-membered, 18-membered, 20-membered, etc) in order to find a receptor that perfectly matches F^- in space.

On the other hand, the interaction of receptor **1** and fluoride anion followed the visible changes of color. The visible color changes may make **1** as a colorimetric sensor. Accordingly, it is possible to conceive the use of this receptor in various sensing applications as well as in other situations such as anion transport and purification, where the availability of cheap and easy-to-make anion receptors would be advantageous.

The above conclusion may have inspiring meaning for us to research new kinds of color receptors and may provide experimental method for the monitoring of fluoride anion in biological system. We believe that the study of 1,4,8,11-tetraazacyclotetradecane-5,7,12,14-tetraone is quite useful for construction of various types of receptors by introducing functional groups at 3′-,3″-, 4′- and 4″- positions or tuning the size of cavity. Further studies on this line are in progress.

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