Anion Recognition Properties of the Neutral Receptors bearing Amide Macrocycle

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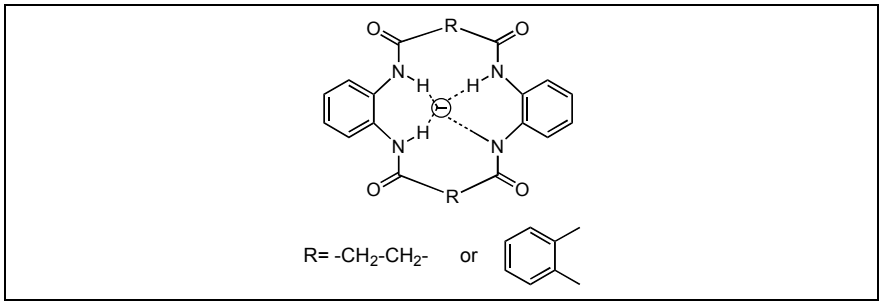

Neutral classes of amide-based macrocycle have been synthesized and the anion binding abilities are assessed by UV-vis titration and ^{1}H nmr experiments. Results indicate that higher anion binding abilities are observed for $H_2PO_4^-$, F^- and AcO^-, but almost no affinity for Cl^-, Br^-, I^- and OH^-. The ^{1}H nmr spectra shows that the interactions between the receptors and fluoride anion depend on two factors, respectively: one is depend on hydrogen bonding, the other on deprotonation.

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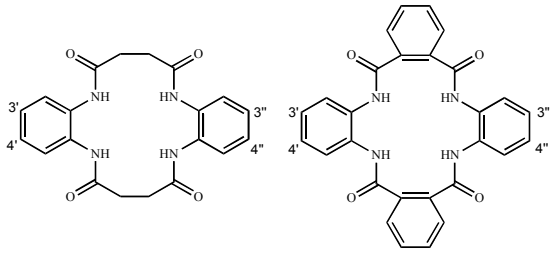
INTRODUCTION

In recent years, increasing attention in the field of host-guest chemistry has been devoted to the fast development of anion recognition systems [1-10]. Considerable attention has focused on the design of anion receptors because of the important roles of anions in bio-medicinal and environmental fields [11]. Anion artificial receptors have represented the unique application prospects in anion sensors [12], phase-transfer catalysts [13], separation and anion-selective electrodes *etc*. [14,15] Synthetic nitrogen-based receptors designed for the selective binding of anions usually consist of either the positively charged ammonium salts, *i.e*., protonated polyamines and/or quaternized amines, or the neutral species such as amide, sulfonamide, pyrrole, urea, and thiourea [16,17]. Hossain *et al*. [18], Szumna and Jurczak [19], and Beer *et al*. [20] have studied the recognition properties of macrocyclic amide systems to different anions. In order to find good macrocyclic receptor matching a certain anion, we designed and synthesized two macrocyclic receptors (Scheme Ⅰ) bearing amides that serve as hydrogen bond donors. The anion binding properties were investigated by UV-vis titration and ^{1}H nmr experiments.

RESULTS AND DISCUSSION

The interactions of **1** and **2** with a variety of anions were investigated through spectrophotometer titrations in DMSO by the addition of the investigated anionic tetrabutyl-ammonium salt to a solution of **1** or **2**.

Scheme I



1 **2**

Figure 1 shows the changes in the absorption spectra of receptors **1** and **2** observed upon the addition of $H_2PO_4^-$. In the absence of anion, the spectrum of compound **1** is characterized by the presence of three peaks at 276, 282, and 300 nm (Figure 1a). The addition of $H_2PO_4^-$ salt results in the decrease of absorption at 300 nm and the increase of absorption at 276, 282 nm. In addition, the presence of a well-defined isosbestic point at 292 nm indicates that the stable complex can exist in a form with certain stoichiometric ratio between the receptor **1** and $H_2PO_4^-$. The addition of F^- and AcO^- induces the similar spectral changes. On the other hand, as exposure to OH^-, Cl^-, Br^- and I^-, these species almost do not bind to receptor **1** appreciably.

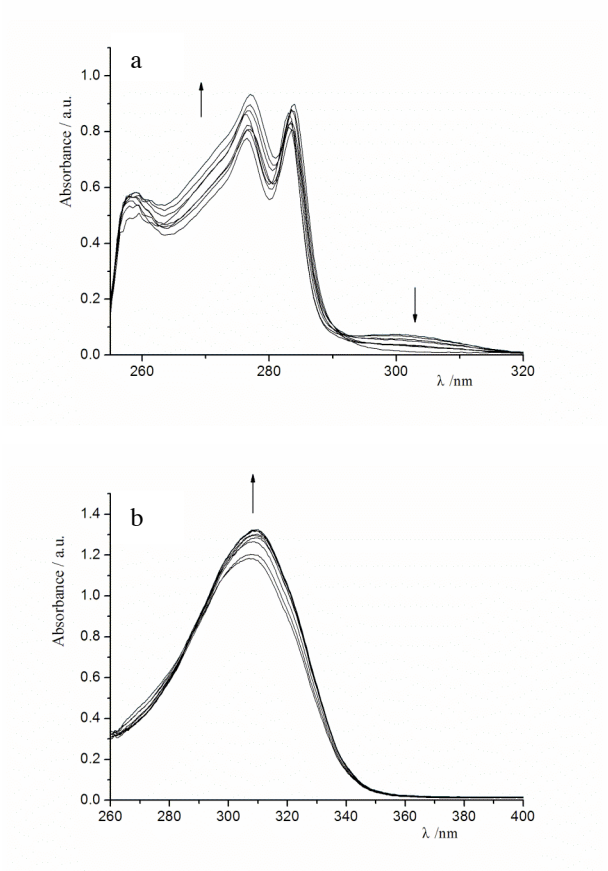


Figure 1. UV-vis spectral changes of receptors **1** and **2** upon the addition of $H_2PO_4^-$ a) **1**, b), **2**; [**1**] = [**2**] = 6.0×10^{-5} mol/L, [$H_2PO_4^-$] = 0–160×10^{-5} mol/L. Arrows indicate the direction of increasing anion concentration.

Compared with receptor **1**, the spectrum of **2** (Figure 1b) is dramatically different. The spectrum of receptor **1** exists two sharp peaks, while that of **2** only shows one broad peak. This can be explained by the fact that receptor **2** is more conjugated than **1** in chemical structure. As shown in Figure 1b, the addition of $H_2PO_4^-$ results in the increase of the absorption band at 310 nm. The additions of F^- and AcO^- induce similar spectral changes. However, the additions of Cl^-, Br^-, I^- and OH^- almost have no effect on the spectrum of receptor **2**.

Job's plots of receptor **1** and **2** with the studied anions in DMSO show the maximum at a molar fraction of 0.5. This result indicates that the receptor**s** bind anion guest with a 1:1 ratio.

Affinity constants of receptors **1** and **2** for anionic species are calculated according to the equation (1) for a 1:1 host-guest complexation [21-24]:

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

where, c_G and c_H are the concentration of guest and host, respectively, X is the absorbance intensity of host after the anion salt is added. X_0 is the absorbance intensity of host before the anion salt is added, K_s is the affinity constant of host-guest complexation, and $\Delta\varepsilon$ is the change in molar extinction coefficient. Then the affinity constants are obtained by the method of non-linear least square calculation and summarized in Table 1.

Table 1

Affinity constants of receptors with various anions.

Anion	K_s(**1**)	K_s(**2**) (M^{-1})
F^-	343.8 ± 0.1	2666.4 ± 0.2
AcO^-	22.5 ± 0.1	340.2 ± 0.1
$H_2PO_4^-$	544.7 ± 0.2	4877.5 ± 0.3
OH^-	<10	<10
Cl^-	<10	<10
Br^-	<10	<10
I^-	<10	<10

Obviously, the anion affinity constants of receptors **1** and **2** are in the order of $H_2PO_4^- > F^- > AcO^- >> OH^- \sim Cl^- \sim Br^- \sim I^-$. Recently, Kim *et al*. [25] have reported results of *ab initio* calculations for cyclic tetra- and hexapeptides and their anion complexes. They have reported that the fluoride anion is indeed well fitted for the 18-membered hexapeptide ring and is located inside the cavity and bound by all six amide hydrogen atoms. As a comparison, the receptors synthesized in this article are 16-membered macrocycle and the cavity may be too small to be fitted by even the F^- anion inside. Thus, F^- anion may be positioned above the 16-membered macrocycle (receptors **1** and **2)** and bound by all four amide hydrogen atoms. So other anions, such as $H_2PO_4^-$, AcO^-, Cl^-, Br^-, and I^- seem also to be too large to fit inside the cavity of receptors. However, for the cavity in receptor **1** and **2**, the interesting fact is that the tetrahedral anion ($H_2PO_4^-$) geometrically may match the receptors better than the trigonal (AcO^-), linear (OH^-), and spherical anions (F^-, Cl^-, Br^-, and I^-) according to the observed affinity constants. Therefore, the configuration of the host-guest complexes is worthwhile to be further discussed later in the text.

On the other hand, the affinity constants of receptor **2** with various anions are higher than that of **1**. This can be explained as follows: 1) The non-conjugated single bonds (C-C) existing in the receptor **1** result in the 16-memered cycle of **1** non-planar. However, the 16-memered cycle of receptor **2** does not contain non-conjugated single bonds (C-C) so that the steric-hinderer acting between receptor **2** and anion is less than between receptor **1** and anions. 2) The electron-withdrawing effect of the four phenyls can enhance the acidity of receptor **2**, resulting in the higher affinity of receptor **2** than that of receptor **1**.

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 [26-30]. According to these reports, there appears one new triplet resonance at 16.1 ppm in ^{1}H nmr spectra, the characteristic resonance of bifluoride (F-H-F),

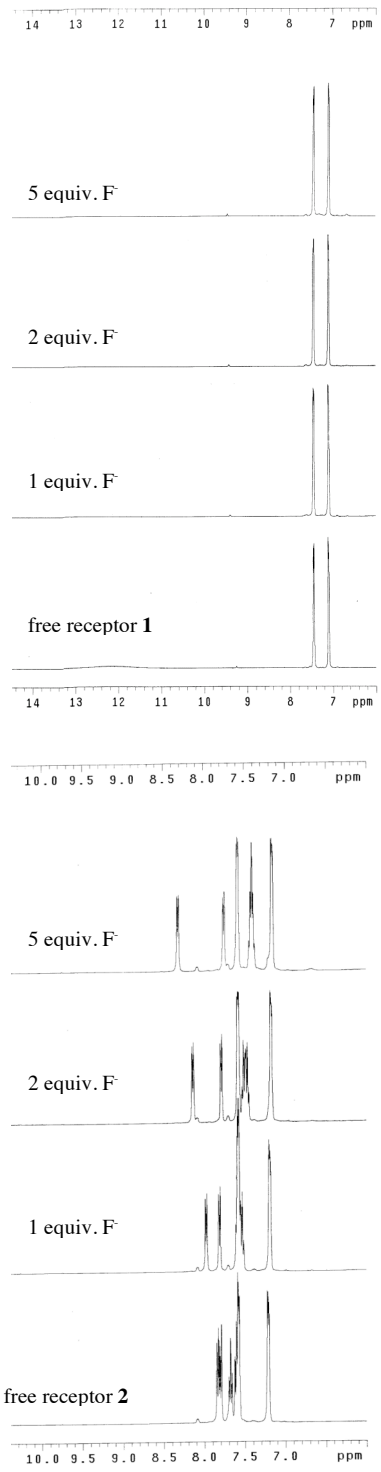


Figure 2. Plots of ^{1}H NMR spectra of receptors (**1** and **2**) in DMSO-d_6 upon the addition of various quantities of Bu_4NF (from 0 to 5 equiv.)

and the proton signals of non-interacted sites shift to the upfield direction. To look into the anion binding properties of receptors **1** and **2** for F^-, ^{1}H nmr titration experiments in DMSO-d_6 are performed (Figure 2). For receptor **1**, the chemical shift of -NH proton (12.2 ppm) broadens gradually and disappears completely during adding of the fluoride anion salt. In addition, no changes of proton shift are observed in the phenyl ring signals (7.5 – 7.1 ppm). This means that receptor **1** interacts with fluoride anion by hydrogen bond (N-H…F). The impact of a weak hydrogen bond on phenyl ring signals is very small, so changes in the chemical shifts of the phenyl ring signals is negligable. However, for receptor **2**, the chemical shift of amide NH (12.4 ppm) disappears completely and the chemical shift of phenyl ring signals moves clearly upfield (from 7.7 to 7.4 ppm) when the fluoride anion salt is added. This phenomenon can be accounted for by the deprotonation of –NH fragment, which brings electron density onto the phenyl rings according to a through-bond mechanism, thus inducing upfield shift [31]. In fact, the increase of electron density in the phenyl rings after deprotonation, causes a shielding effect and should promote an upfield shift. As for the down-field affair of phenyl ring signals at 7.8 ppm, it may also involve the interaction between receptor **2** and anion. Further studies on this line are in progress.

The above results enable us to assume that an anion binding with tetraamide moieties could induce changes in the complex spectrum. Tetrahedral anion ($H_2PO_4^-$) may interact with the receptor by hydrogen bond between three oxygen atoms and the amides. Thus the affinity of $H_2PO_4^-$ with receptor may be the highest among studied anions. Although AcO^- may use two oxygen atoms to form hydrogen bonds, however the hydrogen bond ability of O-H is weaker than that of F-H. So the affinity constant of F^- with receptor is bigger than that of AcO^-. In general, there are two factors that influence the affinity between receptor and anion. One is the degree of configurational match between receptor and anion, and the other is whether the strength of hydrogen bond is strong or weak. To clarify the factors that control the selectivity, further experimental efforts on the spacer molecules may be necessary.

In summary, we have synthesized two anion receptors bearing neutral tetraamide 16-membered macrocycle. The receptors show higher binding ability for $H_2PO_4^-$. When the receptors interact with fluoride anion, the interactions depend on two factors, respectively: one is hydrogen bonding (between receptor **1** and F^-), and the other is deprotonation (between receptor **2** and F^-). However, the affinities and selectivities do not show very clear-cut differences among the anions studied. In order to find the receptor of stronger binding ability and higher selectivity in anion recognition, we may further introduce functional groups at 3'-, 3''-, 4'- and 4''- positions or tune the size of cavity. This will be researched in the future work.

EXPERIMENTAL

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 being dried with $CaSO_4$. Tetra-*n*-butylammonium salts (such as $(n\text{-}C_4H_9)_4NF$, $(n\text{-}C_4H_9)_4NCl$, $(n\text{-}C_4H_9)_4NBr$, $(n\text{-}C_4H_9)_4NI$, $(n\text{-}C_4H_9)_4NAcO$, $(n\text{-}C_4H_9)_4NH_2PO_4$, and $(n\text{-}C_4H_9)_4NOH$) were dried for 24 h in vacuum with P_2O_5 at 333 K before use. C, H, N elemental analyses were made on Vanio-EL. ^{1}H nmr spectra were recorded on Varian UNITY Plus-400 MHz Spectrometer. ESI-MS was performed with MARINER apparatus. UV-vis Spectroscopy titrations were made on Shimadzu UV2550 Spectrophotometer at 298.2±0.1 K. The affinity constants Ks were obtained with non-linear least square calculation method for the data fitting.

Dibenzo[*g*,*o*][1,6,9,14]-tetraazacyclo-hexadecane-[2,5,10,13]-tetraone (1) [32]. 1,2-phenylenediamine (5.4 g, 50 mmol) dispersed in 20-30 mL dioxane was added in portions over 2 h to a vigorously stirred solution of succinic anhydride (5 g, 50 mmol) taken in *ca*. 100 mL dioxane at room temperature. The mixture was heated to reflux for 6 h and the solid formed was collected by filtration and washed with dioxane and methanol then vacuum dried as a fairly air stable microcrystalline product. Yield: 94%. 1H nmr (400 MHz DMSO-d_6) δ12.2 (s, 4H, NH), 7.5(m, 4H, ph-H), 7.1(m, 4H, ph-H), 3.0(m, 4H, CH_2), 2.7(m, 4H, CH_2); *Anal*. Calcd. for $C_{20}H_{20}N_4O_4$ C, 63.2; H, 5.3; N, 14.7. Found: C, 63.0; H, 5.3; N, 14.7. ESI-MS (m/z): 379.01$(M\text{-}H)^-$.

Tetrabenzo[c,g,k,o][1,6,9,14]-tetraazacyclo-hexadecane-[2,5,10,13]-tetraone (2)**.** Solution of 1,2-phenylenediamine (5.4 g, 50 mmol) in dioxane was added dropwise to equimolar solution of phthalic anhydride in the same solvent and stirred for 3 h at room temperature. The solid formed was collected by filtration and washed as mentioned above, and dried in a desiccator over CaO. Yield: 92%. 1H nmr (400 MHz DMSO-d_6) δ12.9 (s, 4H, NH), 7.8(m, 4H, ph-H), 7.7(m, 2H, ph-H), 7.6(m, 6H, ph-H), 7.2(m, 4H, ph-H); *Anal*. Calcd. for $C_{28}H_{20}N_4O_4$ C, 70.6; H, 4.2; N,11.8. Found: C, 71.0; H, 4.2; N, 12.1. ESI-MS (m/z): 475.14$(M\text{-}H)^-$.

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