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Dihydrogen Phosphate Selective Anion Receptor Based on Acylhydrazone

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Anion receptor **1** based on acylhydrazone has been designed and synthesized. UV–vis and ^{1}H NMR titration showed that receptor **1** is selective receptor for dihydrogen phosphate ($H_2PO_4^-$). Dihydrogen phosphate was complexed by the receptor **1** *via* at least 4 hydrogen bonding interactions, contributing from two amide N-Hs and two imine C-Hs. In addition, nitrogen in the aromatic ring could make 2 additional hydrogen bondings with OH groups in the dihydrogen phosphate. However, the receptor **1** could make only 4 hydrogen bonds with halides. Therefore, receptor **1** could bind anions through hydrogen bonds with a selectivity in the order of $H_2PO_4^- > Br^- > Cl^-$ in highly polar solvent such as DMSO.

Key Words : Anion receptor, Acylhydrazone, Hydrogen bonds

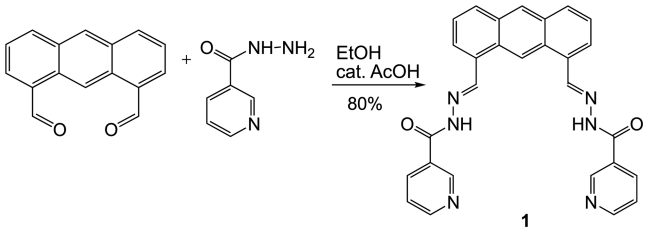
Introduction

The design and synthesis of receptors capable of binding and sensing biologically important anions selectively have drawn considerable attention because anions play a major role in biological, medical, environmental, and chemical sciences[1-13] Recently, many chemical sensor research groups focus the study on recognition of phosphate, as Phosphate is an essential component of chemotherapeutic and antiviral drugs.[14] Moreover, phosphate is becoming a main water pollutant in many countries, and causes serious environmental problem.[15] Because of this, phosphate-binding receptors have become a highly favourable target in molecular recognition chemistry and several systems designed to selectively coordinate phosphate were reported.[16] In designing anion receptors, hydrogen bonds are important anion recognition elements due to their directionality. In designing anion receptors, hydrogen bonds are important anion recognition elements due to their directionality. Most hydrogen bonding anion receptors utilize N-H···anion or O-H···anion hydrogen bonds.[17-19] C-H···anion hydrogen bonds are also utilized for anion binding although the example is rare.[20-27] However, C-H···anion hydrogen bonds play an important role in nature.[28-33]

With these considerations in mind, we introduced anion receptor **1**. Receptor **1** utilizes anthracene as molecular scaffold and acylhydrazone as hydrogen bonding moiety. Receptor **1** makes use of 4 hydrogens from amide N–H and imine C–H. However, additional hydrogen bonds could be utilized between nitrogen in the aromatic ring and OH in the dihydrogen phosphate.

Experimental

The synthesis of the new receptor **1** was obtained as outlined in Scheme 1. Receptor **1** was obtained from the reaction between anthracene-1,8-dicarbaldehyde[34] and nicotino hydrazide[35] in 80% yield.



Synthesis.

Receptor 1: Anthracene-1,8-dicarbaldehyde (62 mg, 0.264 mmol), Nicotinic hydrazide (72 mg, 0.529 mmol) and three drops of acetic acid were dissolved in 25 mL ethanol. The above mixed solution was heated to reflux for overnight and then cooled to room temperature. The formed precipitate was filtered off and washed with ethanol to afford 100 mg (80%) of receptor **1**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.07 (s, 2H), 11.21 (s, 1H), 9.33 (s, 2H), 9.19 (s, 2H), 8.81 (d, J = 3.7 Hz, 2H), 8.79 (s, 1H), 8.34 (d, J = 7.8 Hz, 2H), 8.27 (d, J = 8.7 Hz, 2H), 8.0 (d, J= 6.9 Hz, 2H), 7.69 (t, J = 7.6 Hz, 2H), 7.52 (t, J = 6.1 Hz, 2H) ^{13}C NMR (500 MHz, DMSO-d_6) δ 162.5 152.9 149.3 149.2 135.8 131.8 131.3 130.3 129.5 129.2 128.1 126.1 124.0 122.5 HRMS (FAB, double focusing mass sector) calcd for $C_{28}H_{21}N_6O_2$ $[M+H]^+$: 473.1726, found: 473.1725.

Results and Discussion

Recognition property of the receptor **1** towards dihydrogen phosphate was studied first in DMSO through UV–vis titration spectra. The receptor **1** displayed absorption bands at 268, 299, 409, and 431 nm. Upon addition of increasing amount of dihydrogen phosphate, a moderate increase and decrease in the absorption were also observed depending on wavelength (Figure 1). In addition, multiple isosbestic points emerged at 288, 304, 377, 409, 423, and 434 nm. This result suggests that a typical hydrogen bonding complex forms between receptor **1** and dihydrogen phosphate.

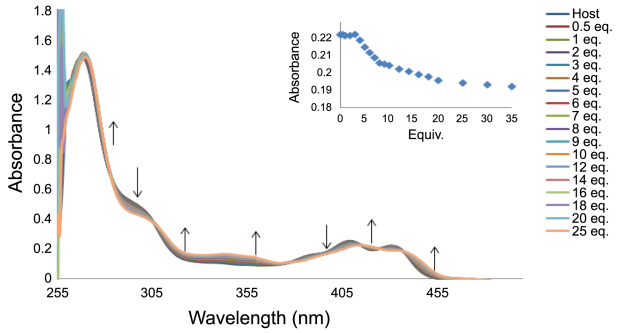


Figure 1. Family of UV-vis spectra recorded over the course of titration of 20 μM DMSO solution of the receptor **1** with the standard solution tetrabutylammonium dihydrogen phosphate.

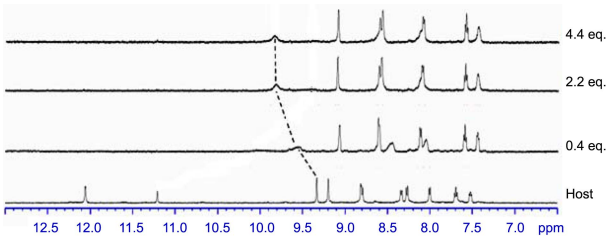


Figure 2. ^{1}H NMR spectra of 2 mM of **1** with increased amounts of tetrabutylammonium dihydrogen phosphate (0-4 equiv.) in DMSO-d_6.

The formation of hydrogen bonding could be confirmed by ^{1}H NMR titration too. The receptor **1** displayed two peaks at 12.05, 11.25 and 9.33 ppm, attributed to amide N-H, anthracene 9-H and imine C-H, respectively. Upon addition of dihydrgen phosphate, N-H peak and anthracene 9-H showed intense broadening. Even imine C-H peak showed line broadening along with downfield shift (Figure 2, dotted line).

We believe that these phenomena were caused by a slow equilibrium between receptor **1** and dihydrogen phospahte. Job plot using ^{1}H NMR in DMSO-d_6 also showed evident 1:1 stoichiometry with receptor **1** (Figure 3). The association constant of dihydrogen phosphate for the receptor **1** could be calculated from Benesi–Hildebrand plot[36] in the case of UV–vis titration and analysis of chemical shift utilizing EQNMR[37] in the case of ^{1}H NMR titration. The association constants calculated were 3.5×10^4 from UV–Vis titration and 3.6×10^4 from ^{1}H NMR titration respectively.

Recognition properties of the receptor **1** towards halides were also studied in DMSO through UV–vis titration spectra. Upon addition of increasing amount of bromide, it was observed that a moderate absorbance decrease at 268 nm along with a moderate absorbance increase at 299, 409 and 431 nm (Figure 4).

In addition, clear multiple isosbestic points emerged at 312, 406, 418 and 427 nm. This result also suggests that equilibrium is established through hydrogen bonding between receptor **1** and bromide. The formation of hydrogen bonding was confirmed by ^{1}H NMR titration too. In DMSO-d_6, both amide N–H peak and imine C–H peak moved to

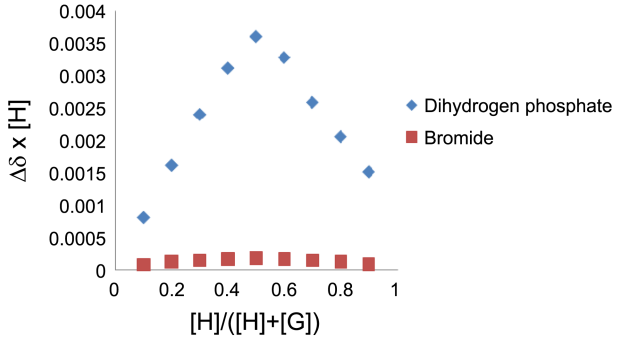


Figure 3. The Job plots of receptor **1** with tetrabutylammonium dihydrogen phosphate and tetrabutylammonium bromide using ^{1}H NMR in DMSO-d_6.

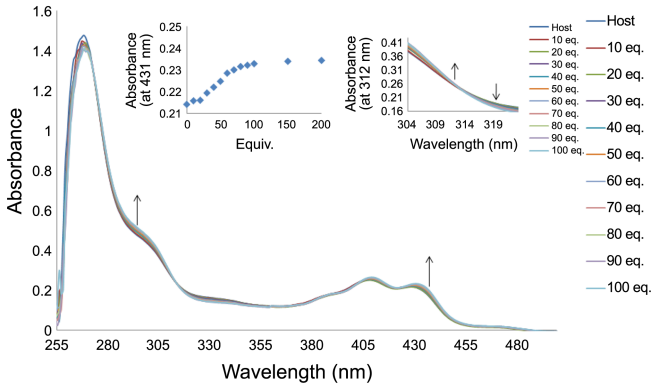


Figure 4. Family of spectra recorded over the course of titration of 20 μM DMSO solution of the receptor **1** with the standard solution tetrabutylammonium bromide.

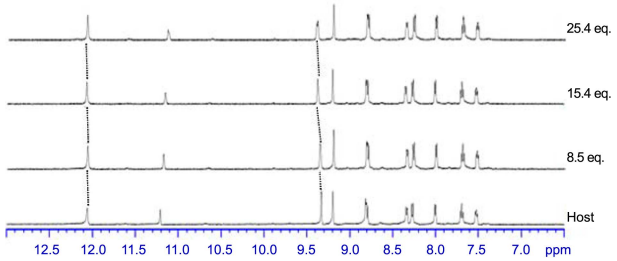


Figure 5. ^{1}H NMR spectra of 2 mM of **1** with increased amounts of tetrabutylammonium bromide (0-25.4 equiv.) in DMSO-d_6.

downfield upon addition of bromide. For example, amide N–H peak moved from 12.05 to 12.07 ppm and imine C–H peak moved from 9.33 to 9.40 ppm (Figure 5).

We believe that such measurable downfield chemical shifts of amide N–H peak and imine C–H peak are caused by the formation of N–H···Br^- and C–H···Br^- hydrogen bonds. Job plot using ^{1}H NMR in DMSO-d_6 showed evident 1:1 stoichiometry between the receptor **1** and bromide (Figure 3) The association constants calculated were 3.3×10^3 from UV–Vis titration and 3.5×10^3 from ^{1}H NMR titration respectively. Other halide such as chloride showed similar behavior with bromide. The binding constants calculated for other halides were summarized in Table 1.

From these experiments, the receptor **1** showed the highest

Table 1. The association constants (M^{-1}) of the receptor **1** with various anions in DMSO[a] (K_a represents association constant through hydrogen bonding, K_{eq} represents deprotonation constant through simple acid-base equilibrium)

Anion	UV		NMR	
	K_a	K_{eq}	[a]K_a	K_{eq}
$H_2PO_4^-$	$3.5 \times 10^4 \pm 1.3 \times 10^2$		3.6×10^4	
CH_3COO^-		$2.2 \times 10^3 \pm 1.3 \times 10^2$		D
F^-		$1.5 \times 10^4 \pm 1.1 \times 10^2$		D
Br^-	$3.3 \times 10^3 \pm 6.3 \times 10$		3.5×10^3	
Cl^-	$6.6 \times 10^2 \pm 1.3 \times 10$		6.9×10^2	
I^-	NC		NC	

[a]Errors in K_a are estimated in less than 10%. NC: Not calculated due to weak binding. D: Decomposed.

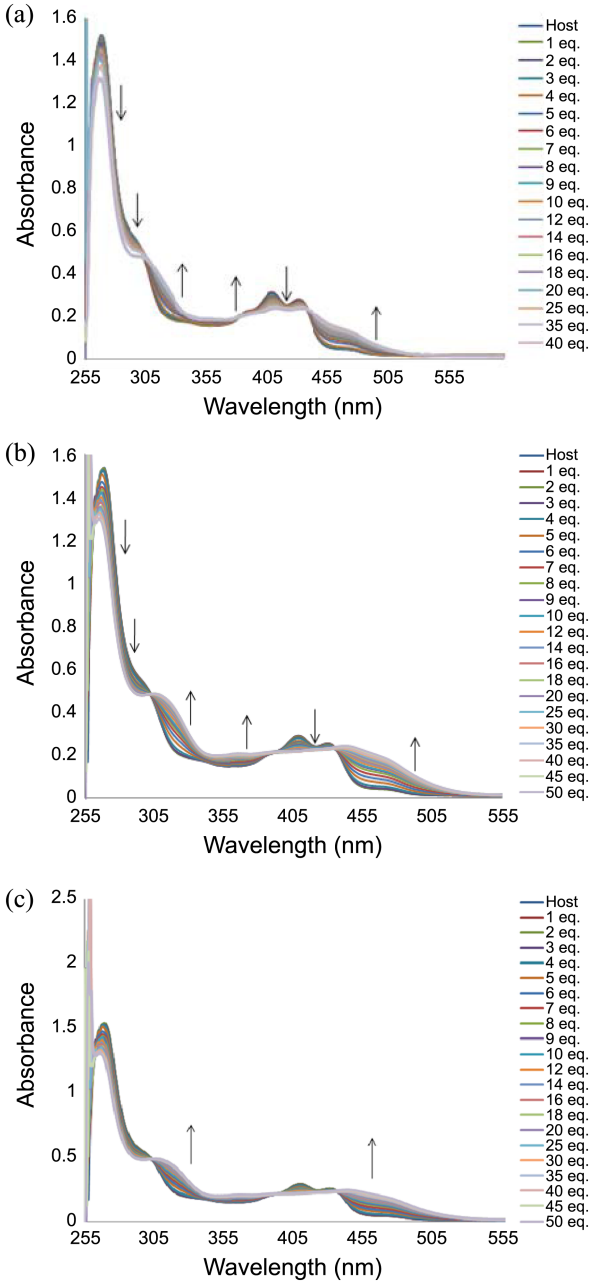


Figure 6. UV-vis spectra recorded over the course of titration of 20 μM DMSO solution of the receptor **1** with the standard solution tetrabutylammonium hydroxide (a), tetrabutylammonium fluoride (b) and tetrabutylammonium acetate.

affinity for bromide among halides. The preference for bromide suggests that the binding cavity is more complementary to the size of bromide ion than the size of other halide ions. As anions have diverse geometries, complementarity between the receptor and anion is crucial in determining selectivity. The complementarity between the receptor and halides is mostly achieved by the size of the receptor binding site due to the spherical shape of halides. Unless the binding site is quite rigid for the size of a particular halide, halide anions tend to associate with receptors according to their basicity (*i.e.*, in the order of $F^- > Cl^- > Br^- > I^-$). However, many examples of size discrimination of halides due to the size of receptor binding site have been reported. In these cases, a better fit dominates the expected higher hydrogen bonding affinity of the hard fluoride for the hard hydrogens.

In order to discriminate hydrogen bonding interaction from deprotonation, UV–vis titration of the receptor **1** with tetrabutylammonium hydroxide was also carried out (Figure 6). The changes in the absorbance spectra with hydroxide were clearly different from those with dihydrogen phosphate. Furthermore, isosbestic poits observed at 296, 389, 417 and 432 nm were different from the isosbestic points observed with dihydrogen phosphate. In addition, the UV–vis spectral changes of the receptor upon addition of excessive fluoride or acetate were nearly identical to those triggered by hydroxide.

Conclusion

In summary, we have designed and synthesized a novel acyl hydrazones based anion receptor anchored at 1,8-

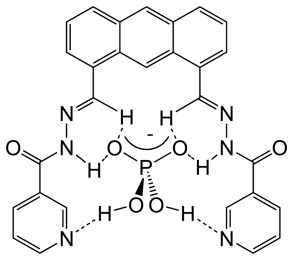


Figure 7. Proposed binding mode of receptor **1** with dihydrogen phosphate.

position of anthracene. UV–Vis and ^{1}H NMR titration showed that receptor **1** is selective receptor for dihydrogen phosphate. Receptor **1** showed strong association constants for dihydrogen phosphate even in polar solvent such as DMSO. In this solvent, dihydrogen phosphate was complexed by the receptor **1** *via* at least 4 hydrogen bonding interactions, contributing from two amide N-Hs and two imine C-Hs. In addition, nitrogen in the aromatic ring could make 2 additional hydrogen bonding with OH groups in the dihydrogen phosphate. Therefore, receptor **1** could have the highest binding affinity for dihydrogen phosphate.

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