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A molecular receptor that selectively binds dihydrogen phosphate

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Abstract—A dihydrogen phosphate-binding receptor (**4**) containing both hydrogen bond donors and acceptors has been prepared by incorporating two pyridyl units to a preorganized biindole scaffold. Receptor **4** strongly and selectively binds dihydrogen phosphate via multiple hydrogen bonds with an association constant (K_a) of 1.1×10^5 M^{-1} in CH_3CN at 22 ± 1 °C. The high selectivity toward the target anion over other anions is proven to be due to two additional hydrogen bonds between the phosphate hydroxyl groups and the pyridyl nitrogens, each of which increases the complex stability by the free energy of 1.6 kcal/mol. This result clearly demonstrates that a selective receptor for a polyprotic anion can be developed by combining both hydrogen bond donors and acceptors.

Anions are ubiquitous in the natural systems and play critical roles in a large variety of chemical and biological processes. In particular, organic or inorganic phosphates are key substrates or intermediates for many biochemical reactions, and are main components of biomolecules such as DNA and RNA. Synthetic receptors[1] capable of selectively recognizing and sensing anions are important tools not only to understand the underlying principles and mechanisms of biochemical processes but also to develop molecular sensors.[2] The receptors have been constructed by introducing hydrogen bond donors because anions are usually good hydrogen bond acceptors. The hydrogen bond interaction is mainly electrostatic in nature and therefore most of the receptors show stronger binding affinities toward more basic anions.

Phosphates exist in four different forms, depending on the pH of the solution. In a weakly acidic or neutral condition, dihydrogen phosphate ($H_2PO_4^-$, $pK_a = 7.21$) is dominant while hydrogen phosphate (HPO_4^{2-}, $pK_a = 12.67$) is the major species in basic solution.[3] Unlike other anions, dihydrogen phosphate contains both hydrogen bond donors and hydrogen bond acceptors. Taking advantage of this structural feature, we herein have prepared a dihydrogen phosphate-binding receptor (**4**) that contains hydrogen bond donors and acceptors in a complementary manner.[4] Receptor **4** strongly binds via multiple hydrogen bonds dihydrogen phosphate with high selectivity over other anions. It has been clearly demonstrated that two additional hydrogen bonds between the phosphate hydroxyl groups and the pyridyl nitrogens are responsible for the high affinity and selectivity.

Unless conformationally rigid, a receptor bearing both donor and acceptor atoms tends to form intramolecular hydrogen bonds, thus the binding site being collapsed. With this in mind, a rigidly preorganized biindole **1**[5] containing two hydrogen bond donors of indole NHs was selected as a building scaffold. Two pyridyl units were incorporated as hydrogen bond acceptors to the biindole scaffold through rod-like, unbendable ethynyl linkers to prevent the collapse of the binding site. Receptor **4** was prepared by Pd/CuI catalyzed Sonogashira coupling[6] of **1** with 2-trimethylsilanylpyridine (**2**), following a literature procedure.[7] Here, only 1 equiv of **2** was used to simultaneously obtain a monopyridyl analogue **3** as a reference, the isolated yields of **3** and **4** being 34% and 33%, respectively (Scheme 1).[8]

The binding properties of **4** with dihydrogen phosphate were investigated by UV/visible spectroscopy. The UV/visible absorption spectra of **4** (2.0×10^{-5} M in CH_3CN) showed bathochromic shifts with clear isosbestic points (334, 372 nm) when the amount of tetrabutylammonium dihydrogen phosphate ($Bu_4N^+H_2PO_4^-$) gradually increases at 22 ± 1 °C. Nonlinear least squares fitting analysis[9] of the titration curve (Fig. 1a), plotting absorbance against equivalent of dihydrogen phosphate, gave

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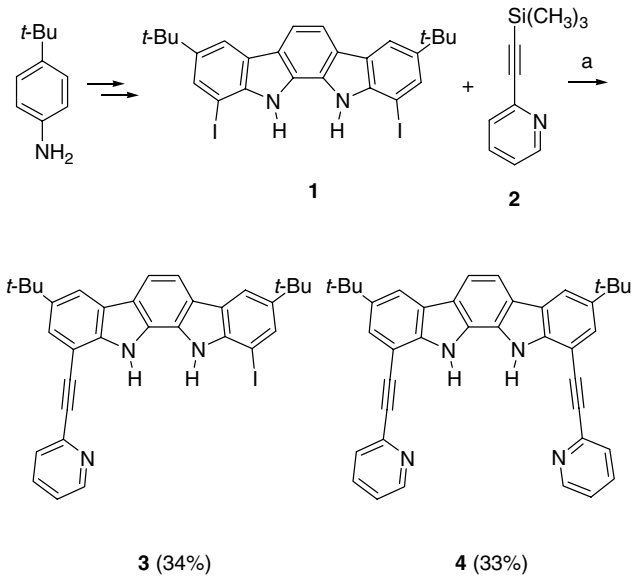

Scheme 1. Synthesis of receptors **3** and **4**. Reagents and conditions:[7] $Pd(PPh_3)_2Cl_2$ (2 mol %), CuI (2 mol %), piperidine, 10 wt % KOH/C_2H_5OH, CH_2Cl_2 room temperature, 12 h.

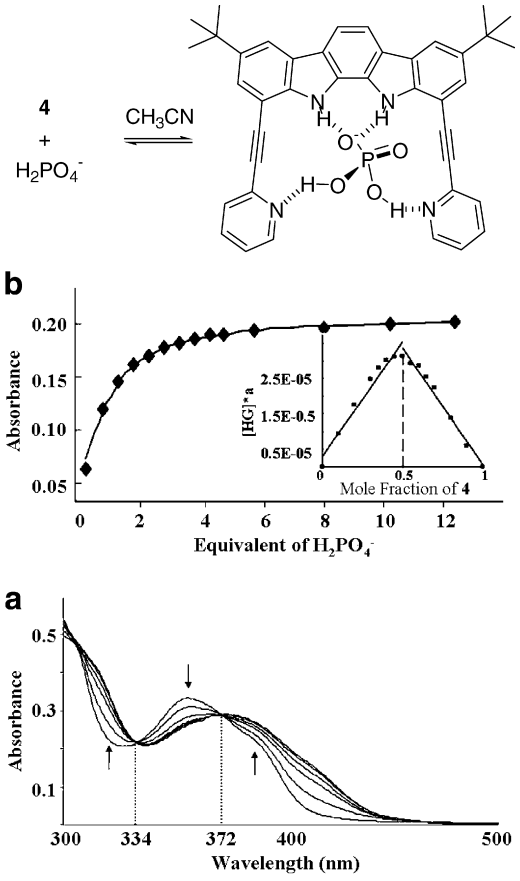

Figure 1. (a) UV/visible spectral changes, and (b) the saturation curve (415 nm) and Job plot (inset) between **4** and tetrabutylammonium dihydrogen phosphate in CH_3CN at 22 ± 1 °C.

the association constant (K_a) of $1.1(\pm 0.15) \times 10^5\ M^{-1}$, the averaged one at three different wavelengths (320, 395, 415 nm). The 1:1 stoichiometry of the complex was confirmed by the continuous variation (Job) method[10] as shown in Figure 1b (inset). The contribution of the pyridyl units to the binding affinity was clearly revealed by employing **1** and **3** as reference receptors bearing no and one pyridyl moiety, respectively. Under identical conditions, the association constants of dihydrogen phosphate were determined to be 500 M^{-1} for **1** and 6800 M^{-1} for **3**. That is, the presence of each pyridyl unit reinforces the binding affinity by approximately 15 times, corresponding to the free energy difference ($\Delta\Delta G$) of 1.6 kcal/mol. This enhancement is apparently attributed to the hydrogen bond between the pyridyl nitrogen and the phosphate hydroxyl group (Fig. 1, top).

Next, the selectivity of receptor **4** for dihydrogen phosphate over other anions was examined. The association constants between **4** and other anions as tetrabutylammonium salts were determined by UV/visible or ^1H NMR titration experiments. For anions such as CN^-, $CH_3CO_2^-$ and HSO_4^-, the former method was used because of severe broadening of the ^1H NMR signals during titration. The results are summarized in Table 1. Due to mainly electrostatic nature of the hydrogen bond, the binding affinity generally increases when increasing the basicity of an anion. This propensity can be seen in a series of halides, showing that the binding affinity increases in the order $Cl^- > Br^- > I^-$. During the ^1H NMR titration, the indole NH signals were greatly downfield shifted ($\Delta\delta$ 2.7 ppm for Cl^-, 2.0 ppm for Br^-, and 0.7 ppm for I^-) upon addition of halides, as a result of the hydrogen bond formation (Fig. 2). It is worthwhile mentioning that the aromatic CH signal of the pyridyl ring was considerably downfield shifted ($\Delta\delta$ 0.85 ppm for Cl^-, 0.75 ppm for Br^-, and 0.35 ppm for I^-), suggesting that halides simultaneously form hydrogen bonds with the aromatic CH protons. This CH hydrogen bond is possibly responsible for the increased binding affinity of **4** (K_a 5000 M^{-1}) with chloride, compared to that (870 M^{-1}) of **1**. As seen in Table 1, dihydrogen phosphate binds much more strongly to **4** than does any other anion, including more basic anions such as cyanide (2100 M^{-1}, pK_a of HCN = 9.21) and acetate (22,000 M^{-1}, pK_a of CH_3CO_2H = 4.76).[3] In addition, it is also interesting to note that the association constant of hydrogen sulfate (1600 M^{-1}, pK_a of $H_2SO_4 = -9$)[3] is similar to that of the much more basic cyanide possibly due to an additional hydrogen bond between the sulfate hydroxyl group and the pyridyl nitrogen atom.

In conclusion, a dihydrogen phosphate-binding molecular receptor that contains both hydrogen bond donors and acceptors has been developed. The receptor strongly binds the target anion with high selectivity as a result of additional hydrogen bonds. This result demonstrates that a receptor for strongly and selectively binding a polyprotic anion can be created by incorporating not only hydrogen bond donors but also acceptors. With the variation of the pyridyl appendage into more optically diverse units, this system can be further modified to a fluorogenic chemosensor capable of selectively recognizing phosphate ions in aqueous solution.

Table 1. Association constants ($K_a \pm 20\%$, M^{-1}) of receptors and anions in CH_3CN at 22 ± 1 °C

Receptor	Anion	K_a (M^{-1})	-ΔG (kcal/mol)
1	$H_2PO_4^-$	500	3.64
3	$H_2PO_4^-$	6800	5.17
4	$H_2PO_4^-$	110,000	6.80
4	Cl^-	5000	4.99
4	Br^-	560	3.71
4	I^-	40	2.16
4	HSO_4^-	1600	4.32
4	CN^-	2100	4.48
4	$CH_3CO_2^-$	22,000	5.86

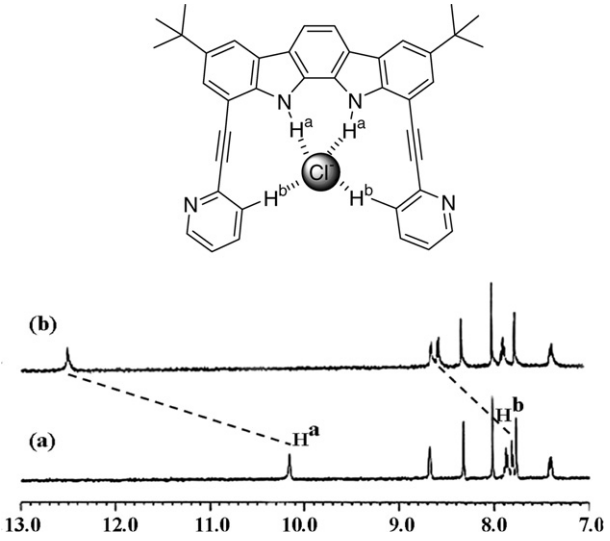

Figure 2. Partial ^1H NMR spectra (400 MHz, CD_3CN, 22 °C): (a) **4**, (b) **4** + $Bu_4N^+Cl^-$ (10.0 equiv), and a proposed structure of complex **4**·Cl^- (top).

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8. Physcial properties and spectral data of molecular receptors. Compound **3**: mp > 300 °C; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 10.72 (s, 1H; NH), 8.99 (s, 1H), 8.68 (d, $J = 4.8$ Hz, 1H), 8.20 (s, 1H), 8.11 (s, 1H), 7.97 (d, $J = 8.2$ Hz, 1H), 7.91 (d, $J = 8.2$ Hz, 1H), 7.81 (d, $J = 1.3$ Hz, 1H), 7.78 (dd, $J = 7.5$, 1.7 Hz, 1H), 7.69–7.65 (m, 2H), 7.33 (m, 1H), 1.49 (s, 9H), 1.46 (s, 9H); MALD-TOF (m/z) $[MH]^+$ calcd for $C_{33}H_{31}IN_3$ 596.16; found 596.16. Compound **4**: mp > 300 °C; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 10.46 (s, 2H; NH), 8.62 (d, $J = 4.8$ Hz, 2H), 8.20 (s, 2H), 7.95 (s, 2H), 7.77 (t, $J = 7.6$ Hz, 2H), 7.68–7.66 (m, 4H), 7.32 (m, 2H), 1.50 (s, 18H); MALD-TOF (m/z) $[M]^+$ calcd for $C_{40}H_{34}N_4$ 570.28; found 570.24.
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