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Highly Effective Fluorescent Sensor for $H_2PO_4^-$

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Abstract: A new anthracene dimer connected by two imidazolium moieties has been systematically designed and synthesized as a fluorescent chemosensor for selective binding of $H_2PO_4^-$ over other anions, which have been examined using fluorescence and ^1H NMR and rationalized with ab initio study.

With the aid of supramolecular chemistry, recognizing and sensing anionic analytes has recently emerged as a key research field.[1] Sensors based on anion-induced changes in fluorescence appear to be particularly attractive due to the simplicity and high detection limit of fluorescence.[2] Noteworthy was a paper by Czarnik and co-workers reporting anthrylpolyamines as PET (photoinduced electron transfer) sensors for phosphate and pyrophosphate in 100% aqueous solution.[3] Other intelligent fluorescent receptors have been utilized for anion-sensing by a number of researchers.[4]

In contrast to well-known types of hydrogen bonding for anion binding such as that found in amide, pyrrole, urea, etc., we have studied the benzene-based tripodal imidazolium receptors utilizing the strong $(C-H)^+\cdots X^-$ charged hydrogen bonding between imidazolium moieties and halide anions.[5] Extending this approach, we have recently reported an anthracene derivative bearing two imidazolium moieties on its 1,8-positions (**1**), which shows selective binding for $H_2PO_4^-$ over other anions when the anions are monitored individually.[5a] Further investigation of the receptor, especially for its binding mode with F^- anion, shows the formation of a 1:2 complex (see Supporting Information). On the other hand, F^- possibly forms a 1:1 complex with **1** in the presence of $H_2PO_4^-$ anions, which is supported by similar theoretical binding energies between **1**:F^- and **1**:$H_2PO_4^-$,[5a] and by strong interference in the experimental fluorescence intensity of $H_2PO_4^-$ upon adding an equimolar amount of F^-. To selectively recognize $H_2PO_4^-$ from other anions and more particularly from F^-, we here report the systematic design, synthesis, and binding study of receptor **2**, an anthracene dimer connected via two imidazolium linkers.

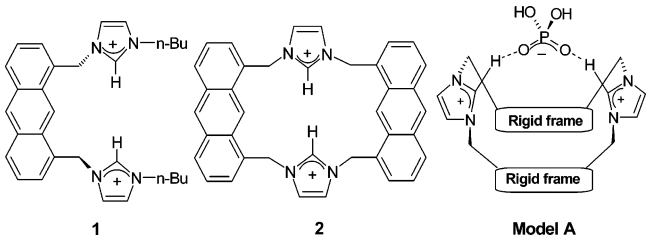

FIGURE 1. Hosts **1** and **2** and a designed molecular system (model **A**).

Due to the high flexibility of the receptor site in **1**, the hydrogen atom of the connecting CH_2 between the anthracene and receptor site also interacts with the F^- anion at a distance of 2.29 Å in addition to the dominant $(C-H)^+\cdots F^-$ charged hydrogen bonding (1.63 Å).[5a] Taking advantage of the directional properties of the partially charged two oxygen atoms in $H_2PO_4^-$, we designed a molecular system (Figure 1, Model **A**) where the receptor site has been immobilized with the help of two rigid frames at both left and right sides avoiding the possible interaction between the hydrogen of the connecting CH_2 and anions. Here the rigid frame could be a fluorophore such as anthracene, etc., or any other ring system. To test and confirm our model, our first attempt was to synthesize a representative host for model **A**. Anthracene, being a fluorophore, has the advantage of being considered as a rigid frame in terms of sensing anions by the change in the fluorophore intensity due to PET mechanism.

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SCHEME 1. Synthesis of Host 2

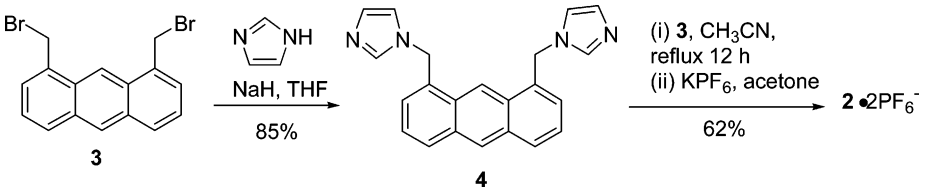

TABLE 1. Calculated Interaction Energies and Experimental Free Energy Changes for the 2-Anion Complexes in kcal/mol[a]

	$H_2PO_4^-$	F^-	Cl^-	Br^-
$-\Delta E^{gas}_{calcd}$	169.49	179.7	149.74	144.95
$-\Delta E^{MeCN}_{calcd}$	16.06	13.32	4.90	4.77
$-\Delta G^{scaled}$	11.24	9.32	3.43	3.34
$-\Delta G^{NMR}_{expt}$			3.57	3.53
K_a (M^{-1})[a]	>1 300 000	340 000	2000	780
$-\Delta G^{flou}_{expt}$	>8.34	7.54	4.49	3.94

[a] Association constants K_a (M^{-1}) were measured using the fluorescence titration. ΔG^{NMR}_{expt} and ΔG^{flou}_{expt} are the changes in Gibbs free energy in an acetonitrile−DMSO (9:1) solution measured by NMR and fluorescence titrations, respectively. ΔE^{gas}_{calcd} is the interaction energy in the gas phase calculated by the B3LYP/6-31(+)G* method. $\Delta E^{MeCN}_{calcd} = \Delta E^{MeCN}_{\mathbf{1}-anion} - \Delta E^{MeCN}_{2MeCN-anion}$, where $\Delta E^{MeCN}_{\mathbf{1}-anion}$ is the interaction energy of the **2**−anion complex in acetonitrile solution based on isodensity surface polarized continuum model (IPCM), and $\Delta E^{MeCN}_{2MeCN-anion}$ is the interaction energy of anion with two acetonitrile molecules in acetonitrile solution. We subtracted the $\Delta E^{MeCN}_{2MeCN-anion}$ value from the $\Delta E^{MeCN}_{\mathbf{1}-anion}$ value in order to establish proper theoretical selectivity of the host for the anions. The ΔG^{scaled} was evaluated by scaling with 70% of the ΔE^{MeCN}_{calcd} for the comparison.

Our synthesis for host **2** begins with 1,8-bis(bromomethyl)anthracene (**3**), which was first obtained from 1,8-bis(hydroxymethyl)anthracene.[6] Compound **3** was then reacted with imidazole using sodium hydride in THF, giving 1,8-bis(imidazolylmethyl)anthracene (**4**) in 85% yield. Reaction of **4** with **3** in acetonitrile followed by anion-exchange with KPF_6 afforded dimer **2** in 62% yield (Scheme 1).

Table 1 illustrates the ab initio calculation results[7] for host **2**−anion complexes. The calculated binding energy of host **2** with $H_2PO_4^-$ is 19.73 and 24.54 kcal/mol larger than those with Cl^- and Br^-, respectively, but smaller than that of F^- by 10.21 kcal/mol. In acetonitrile, the binding energy increases of host **2** in favor of $H_2PO_4^-$ over F^-, Cl^-, and Br^- are 2.74, 11.16, and 11.29 kcal/mol, respectively. Although the host **2**···F^- interaction is (10 kcal/mol) stronger than the host **2**···$H_2PO_4^-$ interaction in the gas phase, the latter is (3 kcal/mol) stronger than the former in the acetonitrile solution, because the F^-···acetonitrile interaction is (7 kcal/mol) stronger than the $H_2PO_4^-$···acetonitrile interaction. Figure 2 shows the optimized structures of the host **2** complexed with $H_2PO_4^-$ and F^-. For both host **1** and host **2** systems, their $H_2PO_4^-$···$(H-C)^+$ distances are almost the same (1.7 Å), and so are their F^-···$(H-C)^+$ distances (1.6 Å). On the other hand, in the host **1** system, the F^-···(H_2C) interaction is moderate (2.29 A), whereas in the host **2** system, the interaction is negligible (>3 Å). Thus, host **1** interacts with F^- more strongly than host **2** does. Consequently, the greater rigidity in host **2** enhances the binding selectivity toward $H_2PO_4^-$.

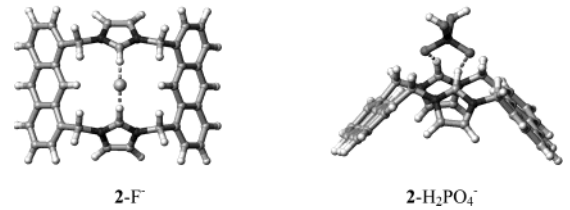

FIGURE 2. Optimized geometry of **2**:F^- and **2**:$H_2PO_4^-$ complexes.

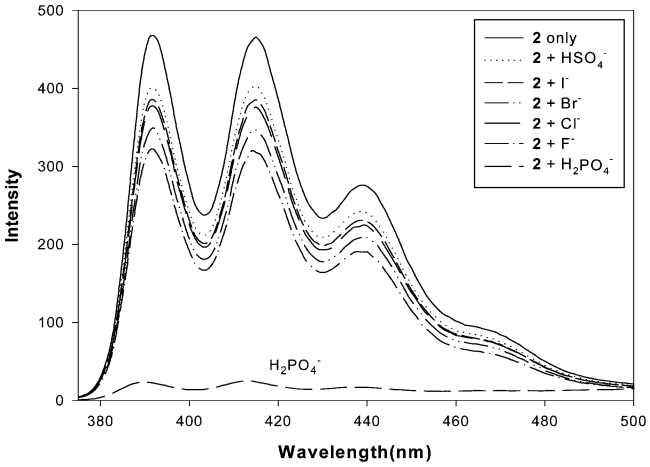

FIGURE 3. Fluorescent emission changes of **2** (6 μM) upon addition of tetrabutylammonium salt of HSO_4^-, I^-, Br^-, Cl^-, F^-, and $H_2PO_4^-$ (10 equiv) in acetonitrile−DMSO (9:1, v/v) (excitation at 367 nm).

As expected, we observed the ^1H NMR spectral change upon adding the anion as tetrabutylammonium salts in acetonitrile-d_3:DMSO-d_6 (9:1). Upon addition of 3 equiv of Cl^- and Br^- to host **2**, large downfield shifts ($\Delta\delta \cong$ 0.138 and 0.110, respectively) have been observed for the C(2) proton of imidazolium moieties, which clearly suggest **2**−anion complexation by CH^+−anion charged hydrogen bonds.

The fluorescence emission changes of **2** upon addition of HSO_4^-, CH_3COO^-, I^-, Br^-, Cl^-, and F^- are illustrated in Figure 3. From the fluorescence titration, the association constants for $H_2PO_4^-$, F^-, Cl^-, and Br^- are observed to be >1 300 000, 340 000, 2000, and 780 M^{-1} (errors < 10%), respectively (Figure 4).[8] The selectivity for $H_2PO_4^-$ ion is more than 600 times those for Cl^- and more than 1000 times that for Br^-. The competitive binding studies of $H_2PO_4^-$ and F^- with respect to **2** using fluorescent

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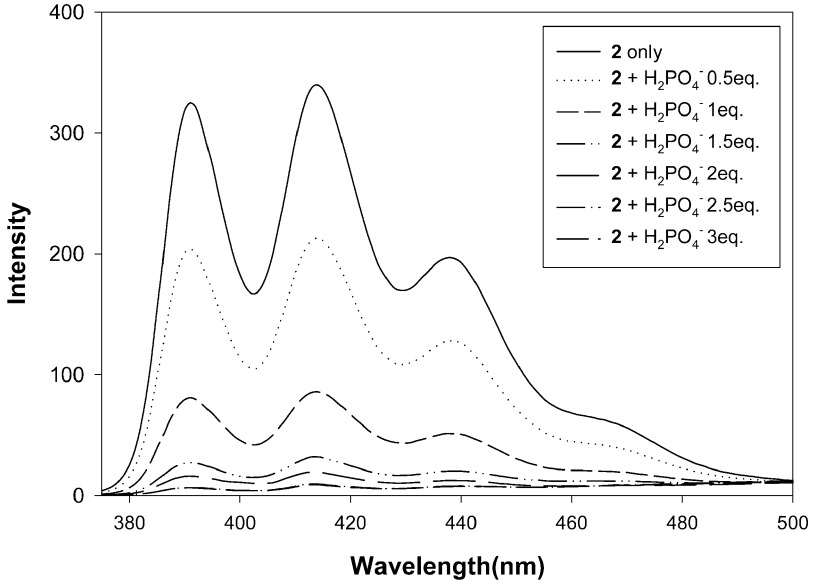

FIGURE 4. Fluorescent titrations of compound **2** (3 μM) with tetrabutylammonium dihydrogen phosphate in acetonitrile−DMSO (9:1, v/v) (excitation at 367 nm).

changes clearly show that there is no interference to the binding of $H_2PO_4^-$ due to the presence of up to 1.5 equimolar concentrations of F^- anions, in contrast to extremely strong interference for the case of host **1** (see Supporting Information).

In conclusion, we have systematically designed the molecular system model **A** in order to selectively recognize biologically important $H_2PO_4^-$. The $(C-H)^+$ group of the imidazolium ring in the receptor sites can optionally be positioned in a host so as to selectively recognize our desired anions. We have shown that our bis-imidazolium anthracene **2** effectively and selectively recognizes the biologically important $H_2PO_4^-$ ion over other anions in aprotic solvents. In particular, these binding phenomena can be monitored via fluorescence quenching effects.

Experimental Section

1,8-Bis(imidazoylmethyl)anthracene (4). To a reaction mixture of imidazole (57 mg, 8.4 mmol) in THF (20 mL) was added NaH (22 mg, 9.2 mmol) at 0 °C. After the reaction mixture was stirred for 20 min at 0 °C, 1,8-bis(bromomethyl)anthracene **3**[6] (100 mg, 0.28 mmol) was added. After additional stirring for 1 h at room temperature, the reaction mixture was poured into 50 mL of water and extracted with $CHCl_3$. The organic layer was then separated, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (1:2, hexanes−ethyl acetate) afforded **4** (81 mg, 85%) as a yellow solid: mp 206−208 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) 8.55 (s, 1H), 8.21 (s, 1H), 8.05 (d, J = 8.6 Hz, 2H), 7.64 (s, 2H), 7.47 (t, J = 6.9 Hz, 2H), 7.30 (d, J = 8.6 Hz, 2H), 7.133 (br s, 2H), 6.97 (br s, 2H), 5.59 (s, 4H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) 137.7, 131.9, 131.3, 129.9, 129.8, 129.5, 128.9, 127.1, 125.4, 119.7, 116.3, 49.5; HRMS (FAB) m/z = 339.1600 $(M + H)^+$, calcd for $C_{22}H_{20}N_4$ = 339.1610.

Dimer (2). To a solution of **4** (170 mg, 0.34 mmol) in acetonitrile (250 mL), 1,8-bis(bromomethyl)anthracene **3** (124 mg, 0.34 mmol) in acetonitrile (100 mL) was added dropwise over a period of 1 h. The resulting solution was refluxed for 20 h. After the solution was cooled, the precipitate was filtered and washed with cold acetonitrile several times. The resulting solid was dried under vacuum and then dissolved in DMF (20 mL). After the reaction mixture was stirred for 20 min at room temperature, 218 mg of KPF_6 (1.08 mmol) was added. After another 12 h of stirring at room temperature, 50 mL of water was added to the reaction mixture. The precipitate was filtered and washed with water. After recrystallization with acetonitrile−ethanol (1:1), a white solid was obtained in 62% yield (175 mg): mp > 310 °C; ^{1}H NMR (DMSO-d_6) δ 8.88 (s, 2H), 8.77 (s, 2H), 8.58 (s, 2H), 8.32 (d, 4H, J = 8.5 Hz), 7.88 (d, 4H, J = 6.6 Hz), 7.69 (t, 4H, J = 6.9 Hz), 7.47 (s, 4H), 5.88 (s, 8H); ^{13}C NMR (DMSO-d_6) δ 135.3, 131.6, 131.3, 130.7, 129.8, 129.1, 128.5, 125.7, 122.2, 117.9, 50.1; HRMS (FAB) m/z = 687.26 $(M - PF_6)^+$, calcd for $[C_{38}H_{30}F_{12}N_4P_2 - PF_6]$ = 687.21.

^{1}H NMR Titration Method. All NMR experiments were performed on a Bruker Avance DPX500 (500 MHz) spectrometer at 298 K. A solution (1 mM) of hosts in CH_3CN-d_3 and DMSO-d_9 (9:1) was titrated with an aliquot of a stock solution (10 mM) of guests as tetrabutylammonium salts in the same solvent. The chemical shift changes of the C(2) proton of imidazolium moieties in hosts were monitored. Data analysis was made using the WinEQNMR computer program. Every titration was repeated at least once until consistent values were obtained.

Preparation of Fluorometric Metal Ion Titration Solutions. Stock solutions (1 mM) of the tetrabutylammonium salts of $H_2PO_4^-$, HSO_4^-, $CH_3CO_2^-$, F^-, Cl^-, Br^-, and I^- in acetonitrile were prepared. Stock solutions of **2** (0.1 mM) were prepared in DMSO. Test solutions were prepared by placing 4−40 μL of the probe stock solution into a test tube, adding an appropriate aliquot of each metal stock, and diluting the solution to 4 mL with acetonitrile and DMSO. For all measurements, excitation was at 367 nm; emission was measured at 420 nm. Both excitation and emission slit widths were 3 nm.

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Supporting Information Available: Experimental Section, a job plot, and fluorescent spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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