An anion receptor with NH and OH groups for hydrogen bonds†

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An anion receptor with NH and OH groups as hydrogen bond donors has been prepared, and both groups are simultaneously involved in hydrogen bonding with anions.

The hydrogen bond is a key interaction for proteins to selectively bind and transport a specific anion in a biological system. As a representative example, the hydrogen-bonding mode between a phosphate-binding protein[1] and hydrogen phosphate is outlined in Fig. 1. Hydrogen phosphate binds by a total of twelve hydrogen bonds: five with the backbone amide NHs, two with guanidinium NHs, one with aspartate, and four with OHs of serine and threonine. Likewise, in a CIC chloride channel[2] the chloride ion was found to be stabilized by hydrogen bonds with OHs of serine and tyrosine, together with the backbone amide NHs of isoleucine and phenylalanine. As mentioned here, not only NH but also OH groups serve as good hydrogen bond donors for binding anions in biological systems.

A large variety of synthetic anion receptors based on hydrogen bonding interactions have been prepared over the last two decades.[3] The NHs of amide, urea, and pyrrole have been extensively introduced as hydrogen bond donors and even acidic CHs have been used. Despite its well-known propensity to form hydrogen bonds, the hydroxyl group has been little utilized for the construction of anion receptors. Kondo and coworkers described anion receptors possessing sulfonamido and hydroxyl groups as the anion-binding moieties.[4] Libra and Scott reported metal salen complexes with four phenolic OHs capable of hydrogen bonding with fluoride.[5] Smith and coworkers investigated the relative binding abilities of 1,2- and 1,3-dihydroxybenzenes with halides.[6] Herein, we report an anion receptor **2** which possesses a binding cavity functionalized with two indole NHs and two aliphatic OHs. Both functional groups are simultaneously involved in hydrogen bonds with anions as demonstrated by ^{1}H NMR spectroscopy and X-ray crystal analysis.

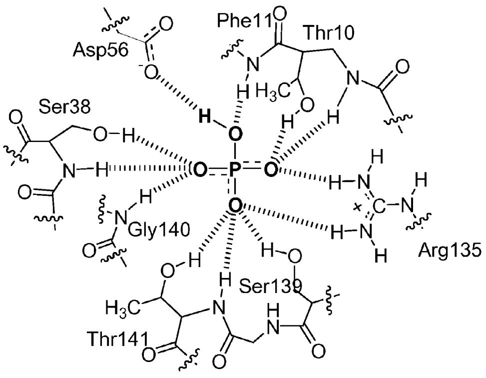
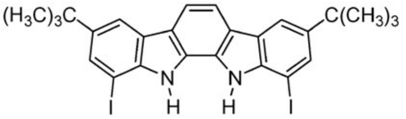


Fig. 1 Hydrogen bonding interactions observed from the X-ray structure between a phosphate-binding protein and hydrogen phosphate.[1a]



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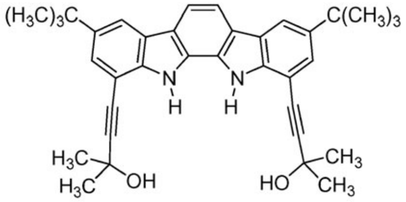

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Compound **1** was prepared from 4-*tert*-butylaniline as described previously.[7] Sonogashira reaction[8] of **1** with 2-methylbut-3-yn-2-ol gave receptor **2** in 80% yield. The binding properties of **2** with anions were first investigated by ^{1}H NMR spectroscopy. Upon addition of anions as tetrabutylammonium salts, signals for NHs and OHs of **2** were greatly downfield shifted in 1% (v/v) H_2O–CD_3CN while the aromatic CH signals were slightly upfield shifted (0.03–0.07 ppm). For example, in the presence of chloride (1 equiv.) the NH signal was shifted from 9.93 to 11.75 ppm and the OH signal was shifted from 3.84 to 5.46 ppm, as the result of hydrogen bonds (Fig. 2).

Slow vapor diffusion of hexane into an EtOAc–CH_2Cl_2 solution of **2** and tetrabutylammonium chloride or dihydrogen phosphate ($\sim$1 equiv.) provided single crystals‡ suitable for X-ray diffraction analysis. In the complex of **2** and $Bu_4N^+Cl^-$ (Fig. 3),[9] the chloride ion is held by four strong hydrogen bonds in the middle of the cavity. The hydrogen bond distances are 3.186–3.303 Å for N(indole)$\cdots$Cl$^-$ and

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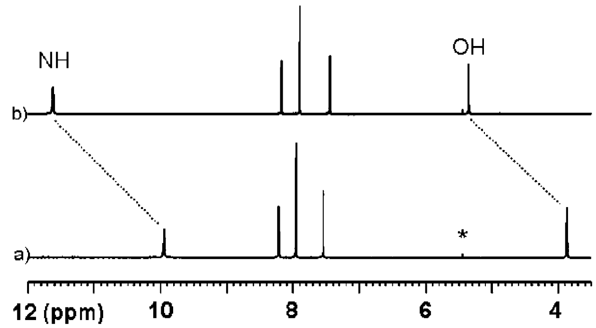

Fig. 2 Partial ^1H NMR spectra (400 MHz, 1% H_2O–CD_3CN, 25 °C) of (a) **2** (2.0 mM) and (b) in the presence of tetrabutylammonium chloride (1 equiv.). The peak marked as * is attributed to residual CH_2Cl_2.

3.114–3.192 Å for O(hydroxyl)$\cdots$$Cl^-$ (see ESI†).[10] In addition, the ethynyl arms are slightly bent (3° to 10°), deviating from the ideal linearity for the sp hybridized carbon possibly to optimize hydrogen-bonding interactions between chloride and hydroxyl groups. It is worthwhile mentioning that tetrabutylammonium cation is located on the aromatic plane close to chloride, possibly due to cation–π interactions as well as electrostatic force.

The crystal structure of **2** and dihydrogen phosphate displays a more complicated and intriguing hydrogen bond network (Fig. 4). The complex exists in a 2+2 dimer in the solid state. Each of the phosphate ions forms six hydrogen bonds; four of them are between receptor and phosphate ion, and two are between the bound phosphate ions. Furthermore, two molecules of each component assemble to give a dimeric complex[11] through five hydrogen bonds: two of O(**2**)$\cdots$HO(**2**), two of (P)O$\cdots$HO(P), and one of (P)OH$\cdots$O(**2**). It should be noted that the hydroxyl groups of **2** serve as both hydrogen bond donor and acceptor in a cooperative manner.[12] The hydrogen bond distances are in the range of 2.616–2.895 Å for O$\cdots$O and of 2.690–2.967 Å for N$\cdots$O, which are comparable to those observed in a ClC chloride channel[2] and synthetic receptors.[13]

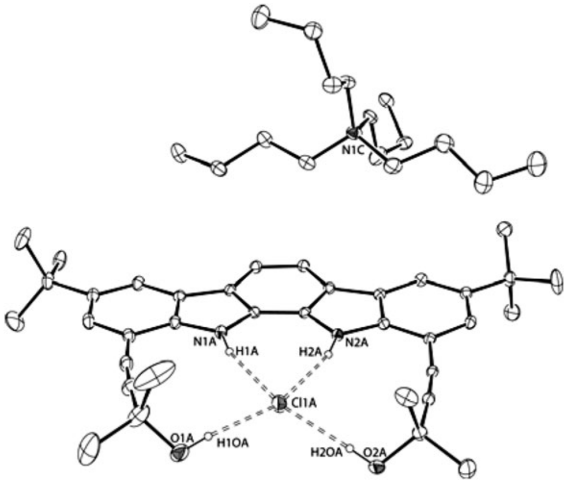

Fig. 3 An ORTEP representation of the X-ray crystal structure of complex $Bu_4N(\mathbf{2}\cdot Cl)$ with 20% probability ellipsoids. The CH hydrogen atoms are all omitted for clarity and hydrogen bonds are shown as dashed lines.

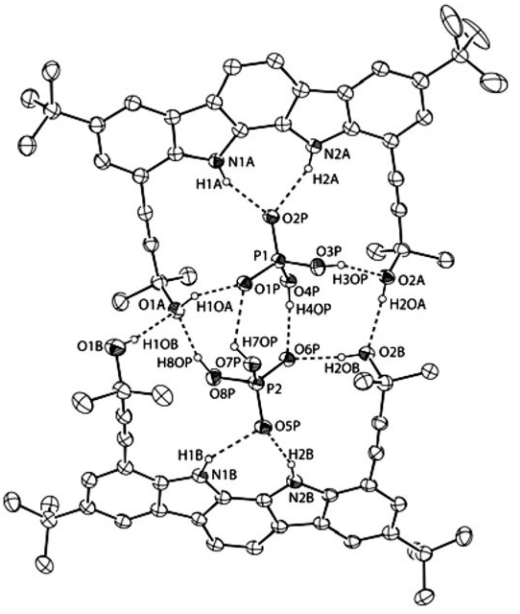

Fig. 4 An ORTEP representation of the X-ray crystal structure of complex $(\mathbf{2}\cdot H_2PO_4)_2^{\,2-}$ with 30% probability ellipsoids. The CH hydrogen atoms are all omitted for clarity and hydrogen bonds are shown as dashed lines. Two tetrabutylammonium cations, not shown here, are located on the aromatic planes, one for each biindole surface (see ESI†).

The binding constants of **1** and **2** with anions were determined in 1% H_2O–CD_3CN by ^1H NMR titration ($K_a < 5 \times 10^3$ M^{-1}) or UV/visible titration ($K_a > 5 \times 10^3$ M^{-1}). Here, a small amount (1%) of water was added in order to minimize experimental errors since in aprotic solvents the binding affinities between **2** and anions appeared to be sensitive to the amount of adventitious water. In the ^1H NMR titrations, the NH and OH signals were gradually downfield shifted and reached saturation as the concentration of an anion increased. The association constant was calculated by nonlinear squares fitting analysis[14] of the titration curves. The NH and OH signals afforded identical binding constants (see ESI†), indicative of two groups participating in the same binding event. As summarised in Table 1, compound **1** which possesses only indole NHs binds anions with association constants of 9 to 210 M^{-1}. Under the same conditions **2** binds anions much more strongly up to the free energy (ΔG) of 21 kJ mol^{-1}, which should be attributed to the additional OH hydrogen bonds.

Table 1 Association constants ($K_a \pm 10\%$, M^{-1}) of **1** and **2** with anions and their ratios in 1% H_2O–CD_3CN at 24 ± 1 °C

Anion	Association constant (K_a, M^{-1})		Ratio of K_a (**2**/**1**)
	1	**2**	
Cl^-	150	56 000	373
Br^-	46	7100	154
I^-	9	280	31
AcO^-	210	1 100 000	5240
$H_2PO_4^-$	44	29 000	660
N_3^-	130	1900	15

The continuous variation method (Job's plot)[15] demonstrated 1 : 1 (or n : n) complexes.

In conclusion, we synthesized receptor **2** which contains a binding cavity functionalized with indole NH and aliphatic OH groups. According to the crystal structures and binding studies, both groups are simultaneously involved in hydrogen bonds with anions, thus greatly increasing the binding stabilities. This result may stimulate the utilization of hydroxyl groups for the construction of more diverse anion receptors.

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Notes and references

‡ Single crystals were obtained by slow vapor diffusion of hexane into an EtOAc–CH_2Cl_2 solution containing 1 : 1 molar ratio of **2** and tetrabutylammonium chloride (or dihydrogen phosphate) over a week. A crystal freshly harvested from the mother liquor of **2** and tetrabutylammonium chloride was coated with paratone oil and the diffraction data were collected at 173 K with a Bruker Smart CCD diffractometer with graphite monochromated Mo-Kα radiation (λ = 0.71073 Å) using the SMART and SAINT software packages.[16] Empirical absorption corrections were applied by use of the SADABS program.[17] A crystal freshly harvested from the mother liquor of **2** and tetrabutylammonium dihydrogen phosphate was coated with paratone oil and the diffraction data were collected at 90 K with synchrotron radiation (λ = 0.70000 Å) on a 4AMXW ADSC Quantum-210 detector with a Pt-coated Si double crystal monochromator at the Pohang Accelerator Laboratory, Korea. The HKL2000 (Ver. 0.98.694) was used for data collection, cell refinement, reduction, and absorption correction.[18] Both crystal structures were solved by direct methods and refined by full-matrix least-squares calculations with the SHELXTL-PLUS software package.[19]

Crystal data for [(tetrabutylammonium)$_2$(**2**Cl)$_2$]·0.5(methylene chloride): $C_{52.25}H_{76.5}Cl_{1.5}N_3O_2$, fw = 831.84 g mol^{-1}, triclinic, space group $P\bar{1}$, a = 16.103(2), b = 17.066(2), c = 22.027(3) Å, α = 112.499(2), β = 90.721(3), γ = 111.326(2)°, V = 5128.2(13) Å^3, T = 173(2) K, Z = 4, μ(Mo Kα, λ = 0.71073 Å) = 0.140 mm^{-1}, 26 506 reflections were collected, 17 623 were unique [R_{int} = 0.0229]. Refinement of the structure converged at a final $R1$ = 0.0655, $wR2$ = 0.1571 for 12 486 reflections with $I > 2\sigma(I)$, $R1$ = 0.0921, $wR2$ = 0.1708, GOF = 1.042 for all 26 506 reflections. The largest difference peak and hole were 0.669 and −0.443 e Å^{-3}, respectively.

Crystal data for [(tetrabutylammonium)$_2$(**2**H_2PO_4)$_2$]·3(methylene chloride): $C_{107}H_{162}Cl_6N_6O_{12}P_2$, fw = 1999.07 g mol^{-1}, monoclinic, space group $P2_1/n$, a = 15.618(3), b = 25.838(5), c = 30.105(5) Å, β = 101.50(3)°, V = 11905(4) Å^3, T = 90(2) K, Z = 4, μ(Mo Kα, λ = 0.70000 Å) = 0.226 mm^{-1}, 80 737 reflections were collected, 21 000 were unique [R_{int} = 0.0595]. Refinement of the structure converged at a final $R1$ = 0.0937, $wR2$ = 0.2489 for 10 239 reflections with $I > 2\sigma(I)$, $R1$ = 0.1593, $wR2$ = 0.2767 for all 59 056 reflections. The structure refinement after modification of the data for the disordered solvent region (2432 Å^3, 20.4% of the crystal volume, 510 solvent electrons per unit cell, which approximately correspond to three CH_2Cl_2 molecules per formula) with the *SQUEEZE* routine of PLATON[20] converged at a final $R1$ = 0.0664, $wR2$ = 0.1843 for 12 812 reflections with $I > 2\sigma(I)$, $R1$ = 0.0975, $wR2$ = 0.2006 for all 21 000 reflections. The largest difference peak and hole were 0.433 and −0.578 e Å^{-3}, respectively. Details of the crystallographic analyses are provided in the ESI. CCDC 674972 and 679730.

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