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Interaction between Biphenols and Anions: Selective Receptor for Dihydrogenphosphate

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Biphenol was shown to bind dihydrogenphosphate ($H_2PO_4^-$) selectively over various other anions ($MeCO_2^-$, Cl^-, Br^-, I^-, NO_3^-, HSO_4^-). The highly selectivity of biphenol toward dihydrogenphosphate is explained in terms of the basicity and shape of the guest anion.

Key words anion recognition; biphenol; dihydrogenphosphate

The recognition and sensing of anions has emerged recently as a key research theme within the generalized area of supramolecular chemistry.[1—3] In the recognition of anions, molecular interaction such as electrostatic interactions, hydrogen bonding, and coordinative bond formation has been widely used. Although hydrogen-donating effects of N–H protons of amide, urea, and thiourea on anion binding have been extensively investigated in the model systems, very few papers have appeared the roles of hydroxyl groups.[4—8] Recently, we reported the investigation of the interaction between quaternary ammonium salts and phenol derivatives, and found the importance of the hydrogen bonding between phenolic hydroxyl groups and the anions in the formation of complexes.[9,10]

Based on our previous work, we conceived an idea to use biphenol derivatives as an anion receptor, because biphenol is constructed from two phenols, which prefer to adopt a twisted conformation and are unable to form intramolecular hydrogen bonding between phenolic hydroxyl groups. Therefore, two phenolic hydroxyl groups of biphenol are expected to efficiently interact with anion species, and the anion selectivity are dependent upon conformational complimentarity between biphenol and the anions.

Biphenol derivatives (**1**—**3**) and a related compound (**4**) were prepared according to the literature[11—13] as follows (Chart 1). 3,3′,5,5′-Tetra-*tert*-butyl-2,2′-dihydroxy biphenyl (**2**) was synthesized by the coupling reaction of 2,4-di-*tert*-butyl phenol using *p*-chloranil at 220 °C for 30 min in 49% yield. The selective elimination of *tert*-butyl group on *ortho* position of **2** using aluminum chloride in nitromethane/benzene gave 5,5′-di-*tert*-butyl-2,2′-dihydroxy biphenyl (**1**) in 80% yield.[11] The methylation of hydroxyl groups of **1** using methyl iodide under basic conditions gave 5,5′-di-*tert*-butyl-2,2′-dimethoxy biphenyl (**3**) in 90% yield.[12] 4,4′-Di-*tert*-butyl-2,2′-methanediyl-diphenol (**4**) was prepared by the hydroxymethylation of *p*-*tert*-butyl phenol with formaldehyde under basic conditions, followed by acid catalyzed condensation of the resultant monohydroxylated *p*-*tert*-butyl phenol with excess *p*-*tert*-butyl phenol in benzene refluxing in 42% yield.[13]

The interaction behavior of biphenols (**1**—**3**) and a related compound (**4**) toward anions (**5**) was investigated by ^{1}H-NMR spectroscopy. In these experiments tetra-*n*-butyl ammonium salts (**5**) having different counter anions (Cl^- (**5a**), Br^- (**5b**), I^- (**5c**), $H_2PO_4^-$ (**5d**), HSO_4^- (**5e**), $CH_3CO_2^-$ (**5f**), NO_3^- (**5g**)) were employed as guests. Upon addition of an equivalent of tetra-*n*-butyl ammonium chloride (**5a**) to **1** in $CDCl_3$ at 24 °C ([**1**]=[**5**]=10 mM), the phenolic OH protons of **1** appeared at 8.07 ppm, far downfield from that of **1** (5.30 ppm), due to its intermolecular hydrogen bonding.[14,15] At this time, upfield shift of the *n*-butyl groups of **5a** was also observed (Fig. 2). The similar downfield shifts of the OH protons were also observed using other anions (**5b** (6.75 ppm at 24 °C), **5c** (5.73 ppm at 24 °C), **5d** (8.44 ppm at −20 °C), **5e** (8.66 ppm at −40 °C), **5f** (too broad to observe the OH signals even at −60 °C), **5g** (7.88 ppm at 0 °C)). To further identify the anion binding mode, ^{1}H-NMR spectra of ammonium salts (**5**) in the presence of three control compounds (**2**—**4**) were measured. Biphenol derivative (**2**) having bulky *tert*-butyl groups on *ortho*-position of phenol moi-

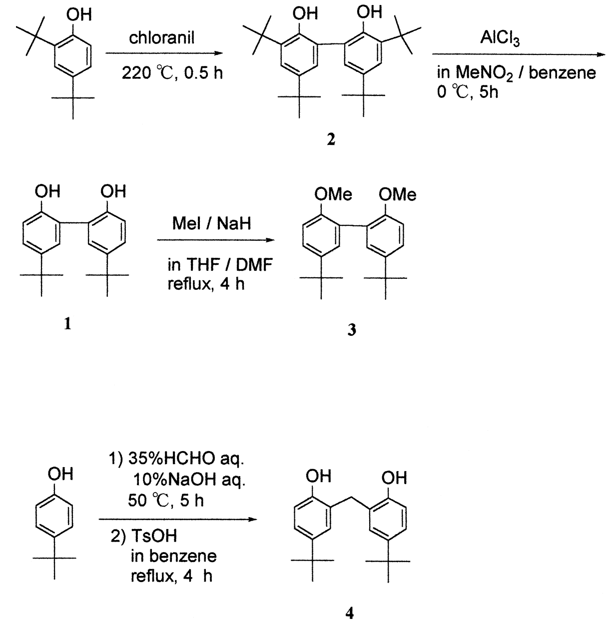

Chart 1

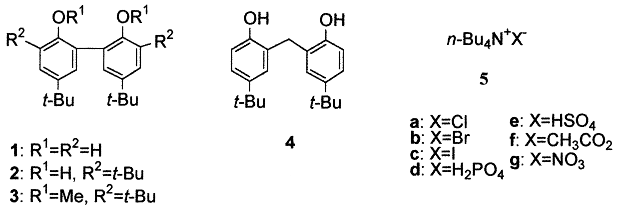

Fig. 1

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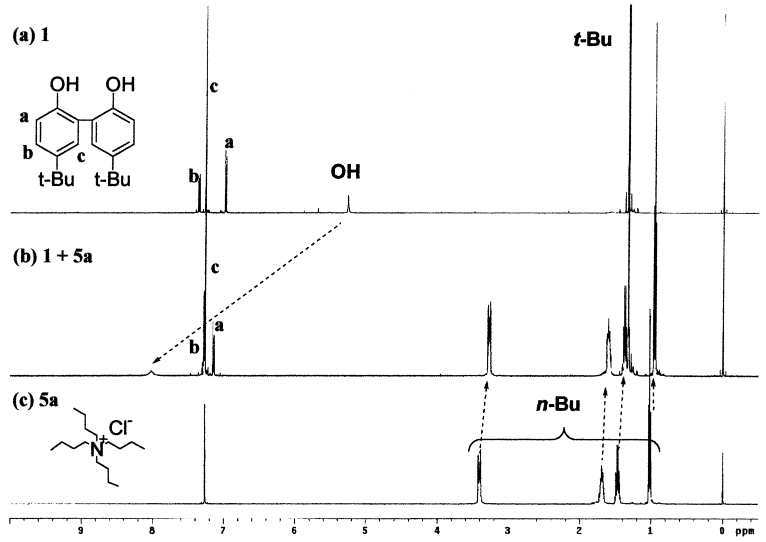

Fig. 2. ^{1}H-NMR Spectra for **1** (a), **1**+**5a** (b), **5a** (c) at 24 °C in $CDCl_3$ ([**1**]=[**5a**]=10 mM)

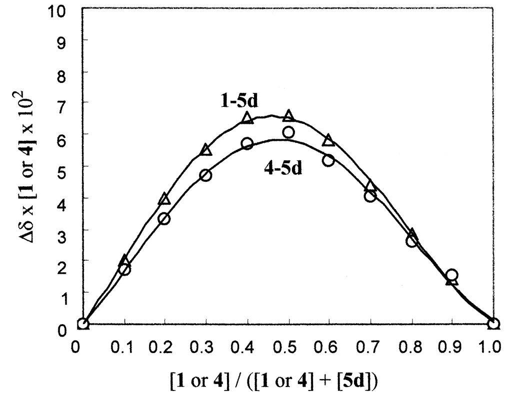

Fig. 3. Job Plots in the Complexation of **5d** and **1** or **4**

eties showed negligible change of the spectra ($\Delta\delta<0.01$ ppm). It is believed to prevent the intermolecular hydrogen bonding between **2** with anion due to the steric hindrance of *tert*-butyl groups adjacent to hydroxyl groups. Analogously, the *O*-methyl derivative (**3**) did not induce any discernible spectral change due to the absence of hydroxyl groups. On the contrary, **4** showed the induced chemical shift in the presence of anions, indicating formation of the complexes, although the degree was smaller than that of **1**.

We estimated the stoichiometry of the complexes (**1**—**5**, **4**—**5**) using the Job plot method.[16] Their 1 : 1 stoichiometry was confirmed by a plot that contains a maximum at the mole ratio of 0.5 in these cases (Fig. 3). Binding constants (K_a) of the receptors (**1**, **4**) with the anion species (**5**) were determined by non-linear least square calculation following the chemical shifts of methyl protons of *n*-butyl groups of ammonium salts by ^{1}H-NMR titration, as shown in Fig. 4.[17,18] From these ^{1}H-NMR titration experiments, receptor (**1**) is more efficient than **4** for all anion species, indicating clearly that biphenol skeleton plays an important role in binding anions (Table 1).[19] It is noted that **1** showed good selectivity for $H_2PO_4^-$ compared with other anions. The anion-binding ability of receptor (**1**) is in the order of $H_2PO_4^-$ (pK_a=2.16 in water)>$CH_3CO_2^-$ (4.76)>Cl^- (−6.1)>NO_3^- (−1.4)>HSO_4^- (−3.1)>Br^- (−9)>I^- (−10). Selectivity trends can be explained by both basicity and shape of the anions. Considering that biphenol prefers to adopt a twisted conformation, the conformational complimentarity between **1** and anions is related to the $H_2PO_4^-$ selectivity. Based on these results, we proposed the plausible structure of the complex (**1**—**5d**) as shown in Fig. 5.

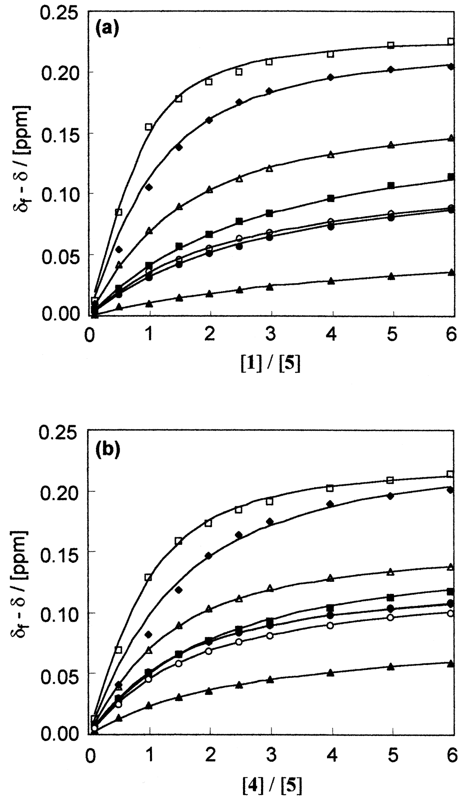

Fig. 4. ^{1}H-NMR Titration of **1** with **5** (a), **4** with **5** (b) at 24 °C in $CDCl_3$

($\delta_f-\delta$) indicates a change in the chemical shift of terminal CH_3 protons of *n*-butyl groups of **5** as a result of added **1** or **4**. Points are experimental and curves are calculated by non-linear regression. □: $H_2PO_4^-$, ◆: $MeCO_2^-$, △: Cl^-, ■: HSO_4^-, ○: NO_3^-, ●: Br^-, ▲: I^-.

In conclusion, we have shown that a novel biphenol receptor system is useful for the recognition of $H_2PO_4^-$. Consider-

Table 1. Association Constants (K_a [M^{-1}] in $CDCl_3$ at 24 °C) for 1 : 1 Complexes of Phenols (**1**, **4**) and Quaternary Ammonium Salts (**5**) and Free Energy ($-\Delta G$ [kJ/mol] in $CDCl_3$ at 24 °C)

Anion[b]		Association constants (K_a) [M^{-1}][a] (free energy ($-\Delta G$ [kJ/mol])) Receptor **1**	**4**
Cl^-	**5a**	310 (14.2)	95 (11.2)
Br^-	**5b**	85 (11.0)	75 (10.7)
I^-	**5c**	11 (5.9)	28 (8.2)
$H_2PO_4^-$	**5d**	1530 (18.0)	210 (13.1)
HSO_4^-	**5e**	95 (11.2)	43 (9.3)
$CH_3CO_2^-$	**5f**	530 (15.5)	70 (10.5)
NO_3^-	**5g**	130 (12.1)	57 (10.0)

a) Errors were estimated to be <10%. *b*) Anions were used as their *n*-Bu_4N^+ salts.

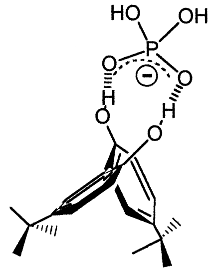

Fig. 5. Plausible Structure of Complex (**1**—**5d**)

ing the high reactivity of phenol moiety, the unique binding motif of biphenol is expected to be use more useful in the development of new anion receptor/sensors with enhanced binding affinity and substrate specificity.

Experimental

^{1}H- and ^{13}C-NMR spectra were measured with a Varian Mercury 200 (200 MHz for ^{1}H, 50 MHz for ^{13}C) and/or an INOVA 500 (500 MHz for ^{1}H, 125 MHz for ^{13}C) spectrophotometer, using tetramethyl silane as an internal standard. IR spectra were collected on a Horiba FT-720 spectrophotometer. Tetra-*n*-butyl ammonium salts (**5**) were purchased from Tokyo Kasei Industries and Kanto Kagaku Co., Ltd. Biphenols (**1**—**3**) and phenol-formaldehyde dimer (**4**) were prepared according to the literature.[11—13]

Job Plot[16] The ^{1}H-NMR sample solutions were made of phenols (**1** or **4**)/quaternary ammonium salts (**5**) under the condition that [**1** or **4**]+[**5**]=10 mM, and [**1** or **4**] varied from 0 to 9 mM in 1 mM steps. The experimentally observed parameter was the ^{1}H-NMR chemical shift ($\Delta\delta$) of methyl protons of *n*-butyl groups of **5** that is sensitive to complex formation.[17] The data were plotted in the form $\Delta\delta\times$[**1** or **4**] *versus* [**1** or **4**]/([**1** or **4**]+[**5**]), and the position of the maximum indicated the stoichiometry of the complex.

^{1}H-NMR Titration Experiemnt[18] Association constants (K_a) were obtained by ^{1}H-NMR titration experiments, performed directly in the NMR tube using a micropipette to add known amounts (0, 10, 50, 100, 150, 200, 250, 300, 400, 500, 600 μl) of a phenol's (**1** or **4**) stock solution (concentration=20.0 mM (**1**) or 82.6 mM (**4**)) in $CDCl_3$ to a solution of quaternary ammonium salt (**5**) (700 μl, concentration=2.88 mM for **1** or 11.9 mM for **4**) in $CDCl_3$. A 1 : 1 association of phenols and quaternary ammonium salts was previously demonstrated, therefore, experimental data were fit to the equation of the 1 : 1 binding isotherm by a nonlinear regression method. All titration experiments were performed in $CDCl_3$ at 24 °C and 500 MHz.

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14) The downfield shift of phenolic OH protons was negligible in more polar solvent such as 10% methanol-d_4 in $CDCl_3$. Such solvent effects are characteristic of interaction involving polar groups and hence support involvement of the phenolic OH group in the interaction with an anion.
15) IR spectra of biphenol (**1**) were measured in the presence or absence of quaternary ammonium salts (**5**) in $CHCl_3$ at 24 °C. With the addition of **5**, the intensity of the initial OH stretching band of **1** at 3550 cm^{-1} decreased and that of a new band around 3400 cm^{-1} increased. The IR spectral change was ascribed to hydrogen bonding between phenolic OH protons and anion component of quaternary ammonium salts.
16) Ogoshi H., Hayashi T., "Encyclopedia of Experimental Chemistry," 4th ed., Vol. 27, ed. by Iguchi H., The Chemical Society of Japan, Maruzen Co., Ltd., Tokyo, 1991, pp. 19—25.
17) Although similar downfield shifts of OH protons were observed for **5d** ($H_2PO_4^-$), **5e** (HSO_4^-), **5f** ($CH_3CO_2^-$), and **5g** (NO_3), the changes of the shifts were not determined accurately because of the exclusive broadening of OH proton signals during titration.
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19) The association constant between *p-tert*-butyl phenol and $H_2PO_4^-Bu_4N^+$ (**5d**) was 405±10 M^{-1}, supporting that the biphenol skeleton was an important factor in the binding of $H_2PO_4^-$ anion.