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ORIGINAL ARTICLE

A new dihydrogen phosphate selective anion receptor utilizing carbazole and indole

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Abstract Dihydrogen phosphate selective anion receptor **2** based on one carbazole and two indole moieties was designed and synthesized. Fluorescence and ^{1}H NMR titration clearly showed that receptor **2** was a good sensor in the selective recognition for dihydrogen phosphate over other anions. Receptor **2** utilized two amide hydrogens, three amine hydrogens to bind anions. These five hydrogens formed concave structure for the selective recognition of dihydrogen phosphate.

Keywords Anion receptor · Carbazole · Indole · Hydrogen bonds

The design and synthesis of receptors capable of binding and sensing anions selectively have drawn considerable attention because anions play a major role in biological, medical, environmental, and chemical sciences [1–9]. As anions display wide range of geometries, design and synthesis of anion recognition motifs are often complicated and require elaborate and sophisticated procedure. Therefore, the development of simple and easy-to-make chemosensors for anions is strongly desired. Among various noncovalent interactions, hydrogen-bonding interactions are particularly useful and effective in designing anion receptor as they are strong and directional. Functional groups such as amides [10–17], ureas [18–22], thioureas [23–31], imidazolium [32] and positively charged groups [33–36] have been widely used to provide hydrogen bonds. To achieve high binding affinity and good selectivity, hydrogen bonding moieties should be arranged in space in a rigid and convergent manner. The correct orientation of hydrogen bonds can differentiate between anionic guests with different geometries. This arrangement has been achieved utilizing various molecular scaffolds. In addition, receptors bearing multiple hydrogen bonding moieties have been shown to be useful to promote cooperative binding, which would result in enhanced binding affinity [37, 38].

Indole has been utilized as hydrogen bonding donor only recently and they have showed high selectivity in discriminating anions. [39–48]. For example, Hu's group designed and synthesized an anion receptor **1** through the condensation of 1,8-anthracene diamine and indole 2-carboxylic acid. The receptor **1** showed high selectivity for fluoride ion over other anions such as acetate and dihydrogen phosphate despite of their similar basicity and surface charge density [49]. This selectivity came from the small cavity formed from two indole moiety and anthracene, which fit the size of fluoride. As anion selectivity results from the correct location and orientation of hydrogen bonds, we envisioned that molecular scaffold arranging indole moiety into larger space would change the selectivity of anion receptor. Therefore, we designed and synthesized the receptor **2**. The receptor **2** utilized carbazole as molecular scaffold and indole as hydrogen bonds moiety. In the receptor **2**, indole-2-carboxylic acid linked to 1,8-position of the carbazole. Compared to Hu's receptor **1** with anthracene molecular scaffold, carbazole arranges two indoles to form wider cavity to bind anions. In addition, N–H hydrogen in the carbazole ring would provide additional hydrogen bonds to the anions. From the experiments, receptor **2** was found to be a selective receptor for

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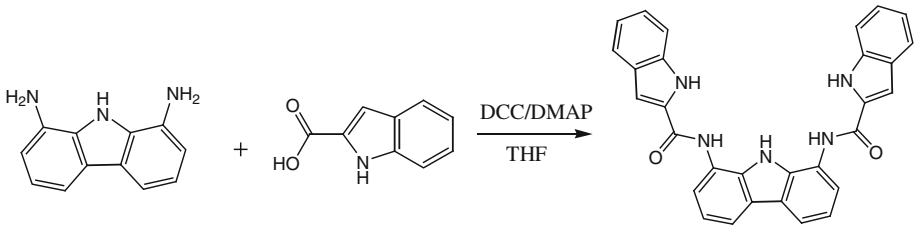
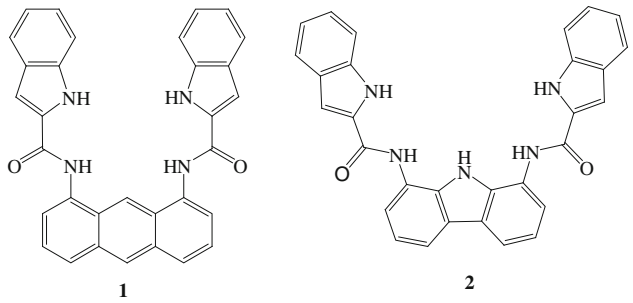
Scheme 1 The synthetic procedure for the anion receptor **2**



dihydrogen phosphate while it did not show any affinity for the halide at all.



1 **2**

The synthesis of **2** was carried out by condensing 1,8-diaminocarbazole with indole-2-carboxylic acid in the presence of DCC and DMAP (Scheme 1).[1]

The receptor **2** displayed strong fluorescence emission in DMSO as shown in Fig. 1. The excitation wavelengths were 301 nm and emission wavelengths were 375 and 456 nm, respectively. The association between the receptor **2** and dihydrogen phosphate was investigated first by fluorescence titration. The intensity of emission spectrum from 20 μM solution of the receptor **2** gradually decreased at 375 nm and increased at 456 nm as the concentration of tetrabutylammonium dihydrogen phosphate salts was increased (1–7 equiv.), which indicates the association between the receptor **2** and dihydrogen phosphate.

The stoichiometry between the receptor **2** and dihydrogen phosphate was determined by Job plot using ^{1}H NMR, which showed evident 1:1 stoichiometry (Fig. 2) [50].

A Benesi–Hildebrand plot [51] by use of change at 456 nm in fluorescence spectrum gave the association

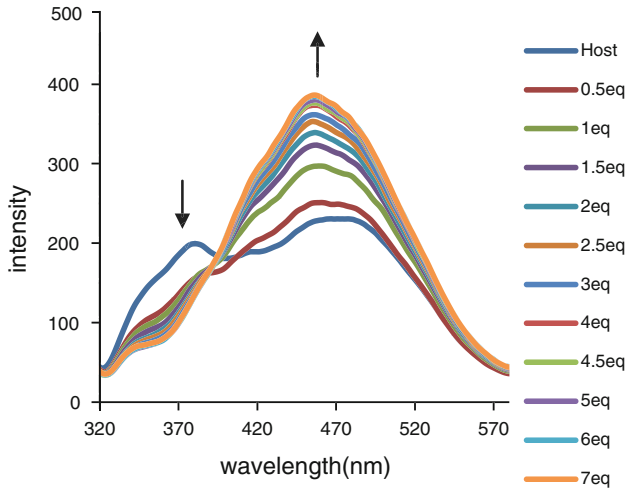


Fig. 1 The change of fluorescence spectra over the course of titration of 20 μM DMSO solutions of the receptor **2** when tetrabutylammonium dihydrogen phosphate was added

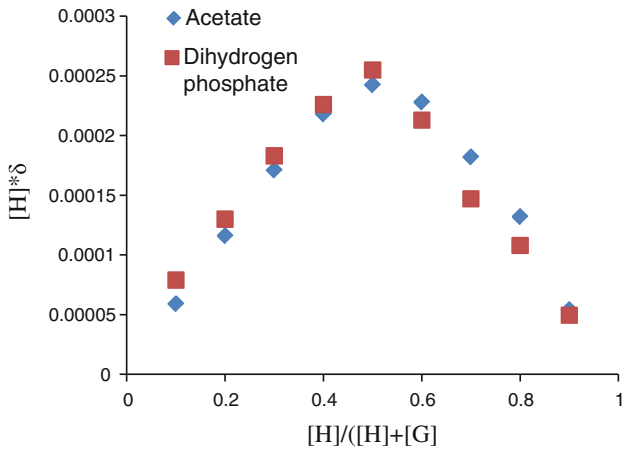


Fig. 2 The Job plots of receptor **2** with tetrabutylammonium dihydrogen phosphate and tetrabutylammonium acetate using ^{1}H NMR in DMSO–d_6

constants. From the experiments, the receptor **2** showed association constant 2.8×10^4 for dihydrogen phosphate in DMSO. This phenomenon could be confirmed by a ^{1}H NMR titration. In DMSO–d_6, all of N–H peaks from indole amine, amide and carbazole amine showed downfield shifts upon addition of dihydrogen phosphate ion. For example,

[1] To a solution of 1,8-diaminocarbazolelx (200 mg, 1.01 mmol) and indole-2-carboxylic acid(488 mg, 3.03 mmol) was added DCC (625 mg, 3.03 mmol) and DMAP (62 mg, 0.50 mmol) under nitrogen condition and stirred for 10 h. After the precipitated solid was filtered, the remained solution was evaporated in vacuo. Recrystallization of remained material with THF and hexane gave the desired product 1 (112 mg) in 22.9% yield. ^{1}H NMR (500 MHz, DMSO–d_6) δ 11.8(s, 2H), 10.7(s, 1H), 10.4(s, 2H), 8.1(d, 2H, J = 8 Hz), 7.7(d, 2H, J = 7.5 Hz), 7.7(t, 2H, J = 8 Hz), 7.5(m, 4H), 7.3(m, 4H), 7.1(t, 2H, J = 7.5 Hz),^{13}C NMR (500 MHz, DMSO–d_6) δ 160.1, 136.9, 133.1, 131.4, 127.1, 124.4, 123.9, 122.5, 121.8, 120.7, 120.0, 119.2, 17.3, 12.5, 104.3 LRMS (ESI): calcd for $C_{30}H_{21}N_5O_2$ *m/e* 438.17; found, 438.15.

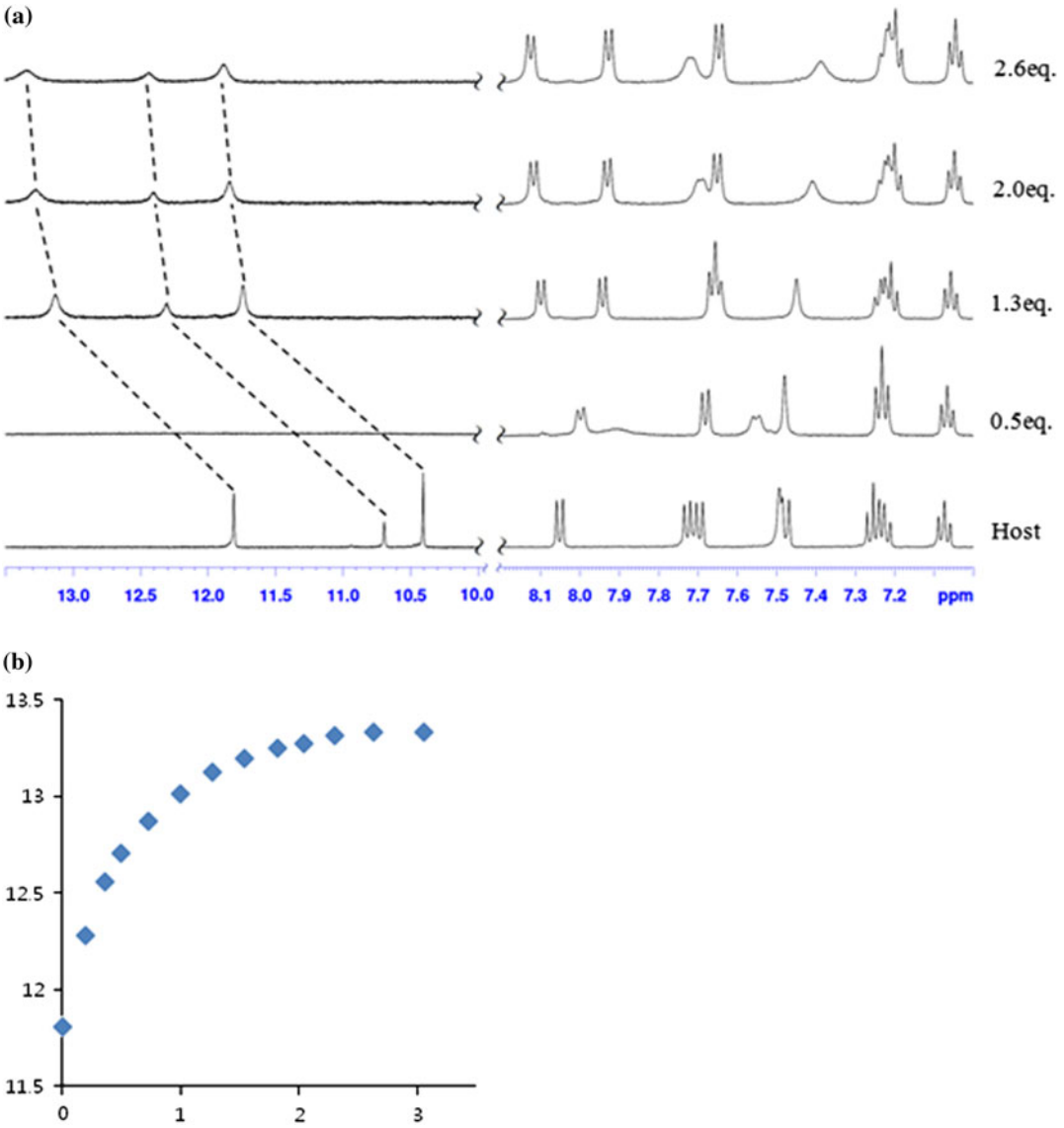


Fig. 3 ^{1}H NMR spectra of 2 mM of **2** with increased amounts of tetrabutylammonium dihydrogen phosphate (0–3 equiv.) in DMSO–d_6 (**a**) and saturation curve of amide N–H peak during titration (**b**)

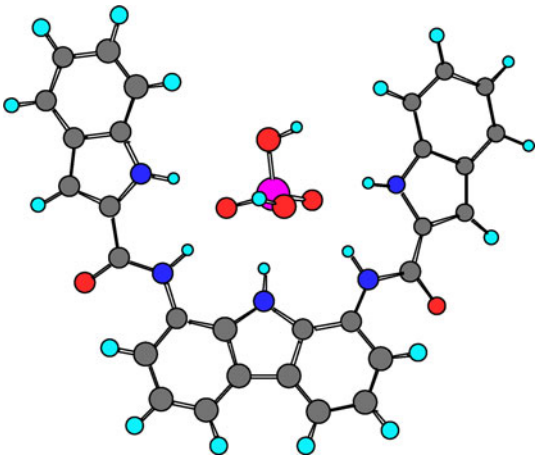


Fig. 4 The energy-minimized structure of receptor **2** and dihydrogen phosphate (Cache 3.2 MOPAC calculation)

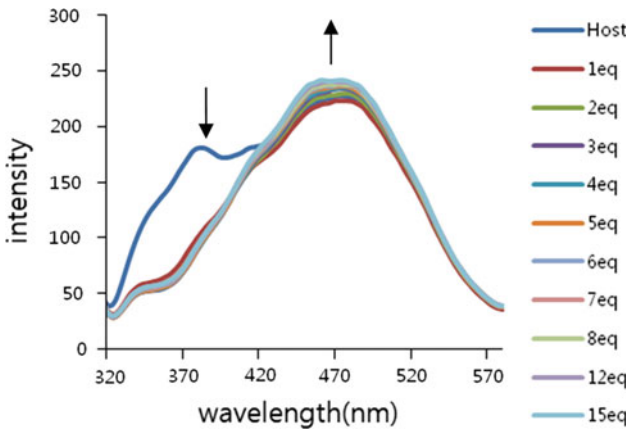


Fig. 5 The change of fluorescence spectra over the course of titration of 20 μM DMSO solutions of the receptor **2** when tetrabutylammonium acetate was added

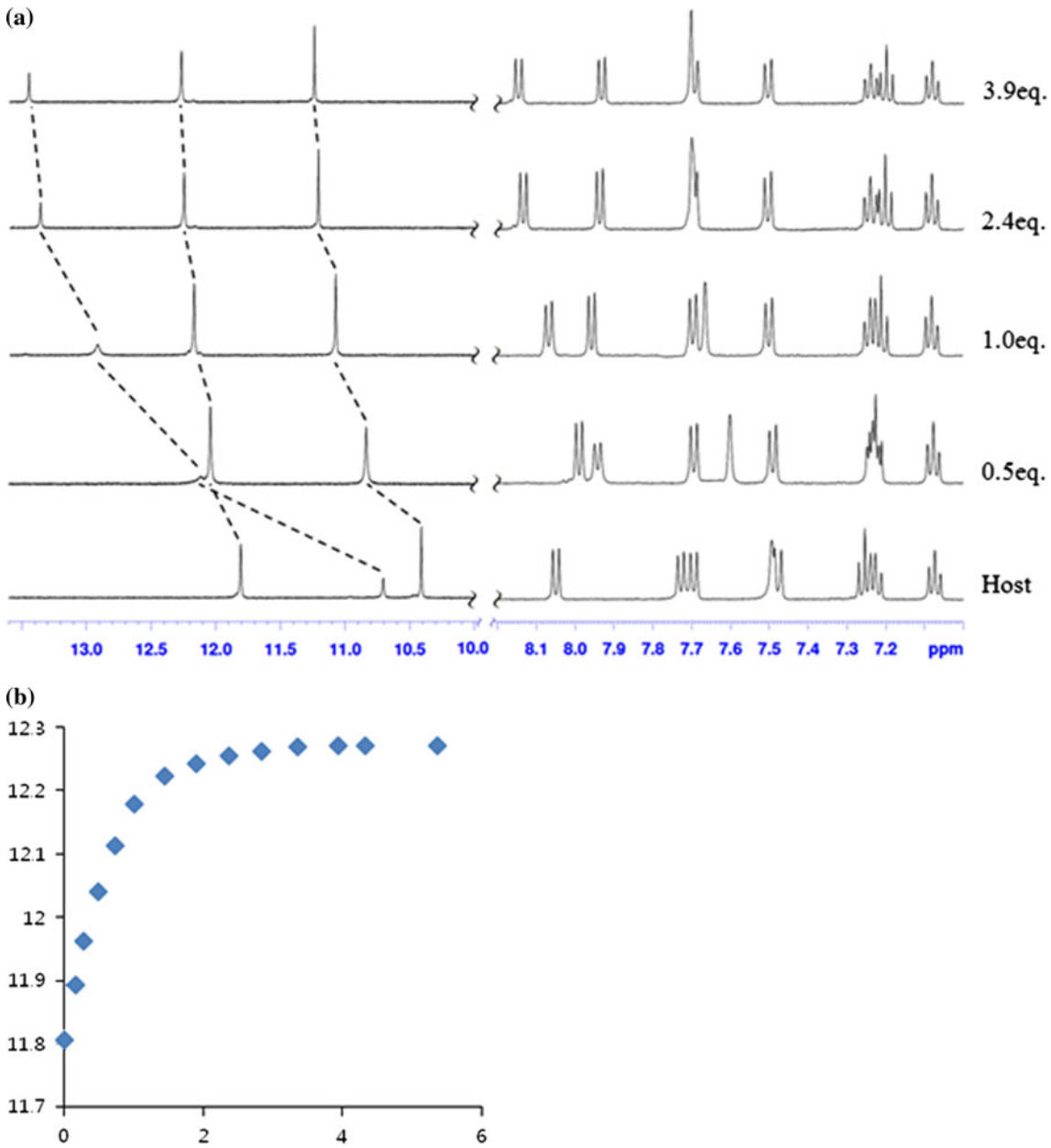


Fig. 6 ^{1}H NMR spectra of 2 mM of **2** with increased amounts of tetrabutylammonium acetate (0–4 equiv.) in DMSO–d_6 (**a**) and saturation curve of amide N–H peak during titration (**b**)

the amide peak of the receptor **2** appearing at 11.8 ppm showed downfield shift until 13.3 ppm. In addition, carbazole N–H amine peak of the receptor **2** appearing at 10.7 ppm showed downfield shift until 12.43 ppm and indole amine peak appearing at 10.4 ppm showed downfield shift until 11.9 ppm (Fig. 3). These downfield shifts indicated that all of these N–H hydrogens participated in the binding event through hydrogen bonds. For titration, amide N–H peak was used. Analysis of chemical shift utilizing EQNMR [52] gave the association constant of 2.9×10^4 M^{-1}, which is similar to the values obtained from fluorescence titrations.

These results are in accordance with the energy-minimized structure of receptor **2** and dihydrogen phosphate (Cache 3.2 MOPAC calculation, Fig. 4). From modeling, the distance between the N–H hydrogen and the dihydrogen phosphate fell in the range 1.90–2.50 Å.

With tetrabutylammonium acetate, a similar phenomenon was observed. In fluorescence titration, the intensity of emission spectrum from 20 μM solution of the receptor **2** gradually decreased at 375 nm and increased at 456 nm again as the concentration of tetrabutylammonium acetate salts was increased (1–15 equiv.) and Job plot showed 1:1 stoichiometry again (Figs. 2, 5). In addition, amide N–H

Table 1 The association constants (M^{-1}) of the receptor **2** with various anions in DMSO

Anion	K_a from Fluorescence titration	K_a from ^1H NMR titration
$CH_3CO_2^-$	6.8×10^3	$5.9 \times 10^{3\dagger}$
$PhCO_2^-$	–	$1.4 \times 10^{3\dagger}$
NO_3^-	nb‡	nb
$H_2PO_4^-$	2.8×10^4	$2.9 \times 10^{4\dagger}$
HSO_4^-	nb	nb
ClO_4^-	nb	nb
Cl^-	nb	nb
Br^-	nb	nb
I^-	nb	nb

nb No binding

† Errors are less than 10%

hydrogen, indole amine N–H hydrogen and carbazole N–H hydrogen showed downfield shifts again.(Fig. 6). From these experiments, association constants for acetate were calculated as 6.8×10^3 and 5.9×10^3 from the fluorescence titration and ^1H NMR titrations, respectively.

We also investigated association constants of other anions. The results are summarized in Table 1. Among the anions investigated, the receptor **2** showed good selectivity for dihydrogen phosphate. The fluorescence intensity changes were the most significant with dihydrogen phosphate. Probably the receptor **2** has more preorganized structure to accept dihydrogen phosphate than other anions.

As the receptor **2** had lager cavity size than that of the receptor **1**, and different location and orientation of hydrogen bonds induced by carbazole imparted big differences of anion selectivity, the receptor **2** showed stronger affinity towards dihydrogen phosphate while the receptor **1** showed stronger affinity for fluoride than other anions.

In summary, we have developed a dihydrogen phosphate selective anion receptor **2** based on one carbazole and two indole moieties. Receptor **2** utilized two amide hydrogens, one amine hydrogen from carbazole and two amine hydrogens from indole to bind anions. As the binding cavity formed from these hydrogens is different from that of the receptor **1**, the selectivity of the receptor **2** for the anion is quite different from that of the receptor **1**. The receptor **2** binds anions through hydrogen bonds with a selectivity of $H_2PO_4^- > CH_3CO_2^- > C_6H_5CO_2^-$ while the receptor **1** binds anions only fluoride.

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