J Incl Phenom Macrocycl Chem (2013) 76:119–124
DOI 10.1007/s10847-012-0180-2

ORIGINAL ARTICLE

A new anion receptor with biquinoline molecular scaffold

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Received: 27 February 2012 / Accepted: 12 May 2012 / Published online: 10 June 2012

Abstract We have designed and synthesized a new fluorescent receptor **3** utilizing biquinoline as a molecular scaffold. The receptor **3** has two amide hydrogens and two carbamate hydrogens anchored at 4,4′-position of biquinoline. Fluorescence and ^{1}H NMR titration showed that receptor **3** bound anions with different stoichiometry depending on the shape of anions and its association constants for anions reflected the basicities of anions. Receptor **3** bound chloride, acetate and benzoate in 1:2 stoichiometry and had a highest affinity for acetate. Tetrahedral shaped dihydrogen phosphate bound receptor **3** in 1:1 stoichiometry, although its affinity was low.

Keywords Anion receptor · Hydrogen bond · Biquinoline

There have been considerable efforts to develop efficient artificial receptors for anion recognition and sensing as anions play a major role in biological, medical, environmental, and chemical sciences [1–9]. Especially, fluorescent anion chemosensors are of great importance because of their high sensitivity and low detection limit [8, 10–14]. Therefore, many chemical sensors follow the approach of the covalent attachment of signaling subunits and binding sites [15, 16]. Chromogenic or fluorogenic groups that are covalently linked to the receptor moiety as signaling subunits and multiple hydrogen-bonding interactions as binding sites have been frequently utilized. Among many fluorogenic groups, biquinoline attracted our interest. With suitable modification, it could not only provide a molecular scaffold to arrange anion binding site but also provide a fluorescence reporting group. Furthermore, it could provide metal ion recognition site. Therefore, it could be used as a ditopic receptor. However, it has rarely been used for the anion recognition although it was utilized to report host–guest binding [17].

Here, we would like to report the synthesis and binding properties of a new anion receptor **3** utilizing biquinoline as a molecular scaffold. This receptor has two amide hydrogens and two carbamate hydrogens anchored at 4,4′-position of biquinoline. We expected that these four hydrogens would form a concave structure for anions. However, the receptor **3** was found to bind most of anions in a 1:2 stoichiometry except dihydrogen phosphate.

The synthesis of a new receptor **3** was obtained as outlined in Scheme 1. Ethylenediamine was protected with di-tert-butyl dicarbonate to give compound **1**. Then compound **1** was reacted with 2,2′-biquinoline-4,4′-dicarboxylic chloride **2** to give the desired anion receptor **3** in 38 % yield. 2,2′-Biquinoline-4,4′-dicarboxylic chloride was obtained from the reaction between 2,2′-biquinoline-4,4′-dicarboxylic acid and thionyl chloride.[1]

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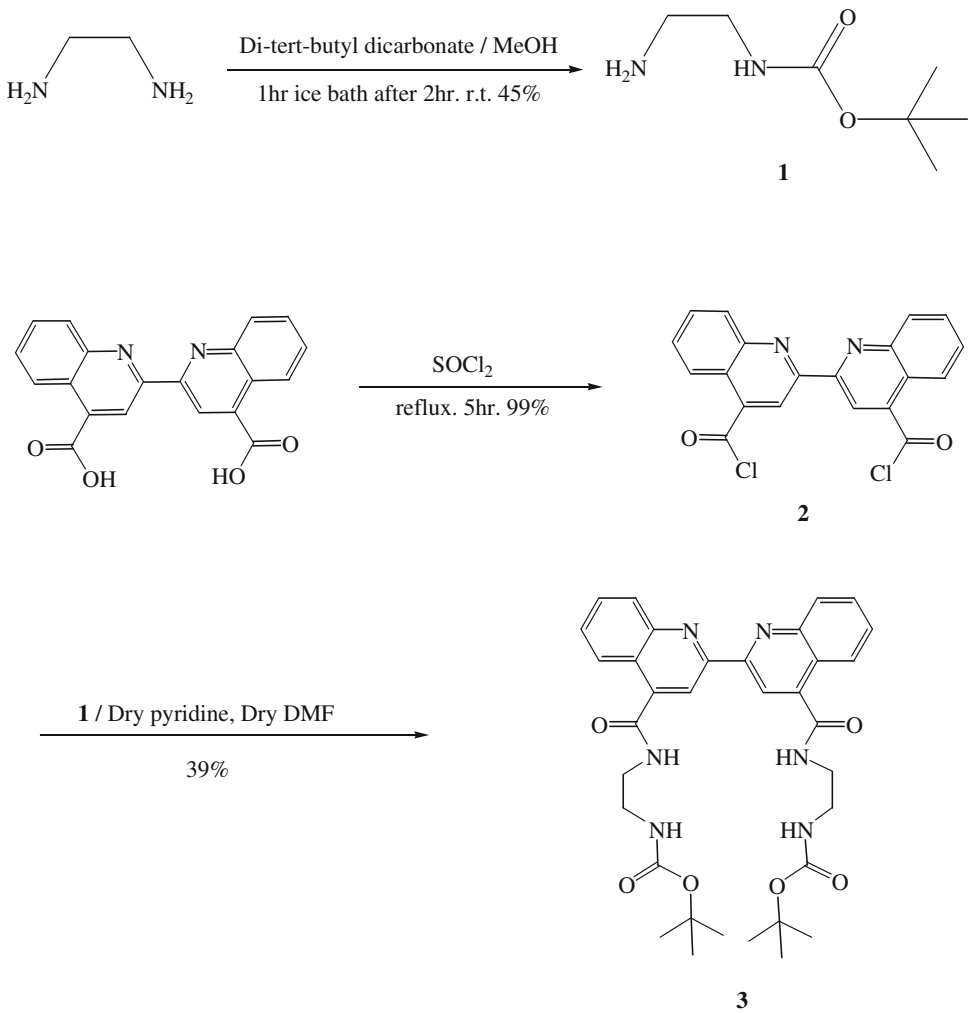
[1] Synthesis of compound **1**: To a solution of di-tert-butyl dicarbonate (1.6 g, 7.49 mmol) in methanol (5 ml) was added ethylenediamine (500 mg, 8.3 mmol) at 0 °C. The solution was stirred for an hour and the solution temperature was raised to room temperature slowly. After the solution was stirred for 4 h more, the precipitated solid was removed through filtration. Evaporation of the liquid layer and silicagel chromatography of the residue with 50 % methanol in dichloromethane gave the compound **1** (1.54 g) in 88 % yields. ^{1}H NMR ($CDCl_3$, 500 MHz): 5.37(s, 1H), 3.26(s, 2H), 3.03(m, 2H), 2.64 (t, J = 6.0, 2H), 1.30 (s, 9H). Synthesis of compound **3**: The

Scheme 1 The synthetic scheme for anion receptor **3**



Receptor **3** displayed strong fluorescence emission in DMSO as shown in Fig. 1. The excitation and emission wavelength were 332 and 383 nm, respectively. The association between receptor **3** and acetate was investigated first by fluorescence titration. The fluorescence change of receptor **3** was monitored in DMSO. The intensity of emission spectrum from 20 μM solution of receptor **3** gradually increased as the concentration of tetrabutylammonium acetate salt was increased (10–360 equiv.), which indicated the association between receptor **3** and acetate. In addition, the saturation curve of fluorescence spectrum showed two saturation points (Fig. 1b). The stoichiometry between receptor **3** and acetate was determined by Job plot using fluorescence spectroscopy, which showed evident 1:2 host–guest stoichiometry (Fig. 2) [18] as expected from the saturation curve. A Benesi–Hildebrand plot by use of change in the 383 nm fluorescence intensity gave the association constant [19]. From the experiments, receptor **3** showed association constant ($\beta_2 = K_1K_2$) 2.8 × 10^5 for acetate in DMSO.

Footnote 1 continued
suspension of 2,2′-biquinoline-4,4′-dicarboxylic acid(150 mg, 0.44 mmol) in thionyl chloride (10 ml) was refluxed for 5 h. After all of starting material was dissolved, the reflux was stopped and all of thionyl chloride was evaporated in vacuo to give compound **2**. The remained material was directly used for next reaction without purification. The remained material was dissolved in dried DMF (10 ml). Then the compound **1** (209 mg, 1.31 mmol) in dried pyridine (8 ml) was added to this solution in ice bath and the solution temperature was raised to room temperature slowly. Then the reaction mixture was stirred for 2 h. Filtration of precipitated solid gave the desired compound **3** (105 mg) in 38 % yields. ^{1}H NMR (DMSO-d_6, 500 MHz) 8.98(t, J = 5.5, 2H), 8.82(s, 2H), 8.27(d, J = 8.0, 2H), 8.22(d, J = 8.0, 2H), 7.91(t, J = 8.0, 2H), 7.73(t, J = 8.0, 2H), 6.97(t, J = 5.5, 2H), 3.45(m, 4H), 3.25(m, 4H), 1.40(s, 18H) ^{13}C NMR(500 MHz, DMSO-d_6) 166.81, 155.75, 154.41, 147.53, 143.79, 130.47, 129.67, 128.12, 125.74, 124.56, 116.19, 77.68, 28.26 two peaks are hidden in DMSO solvent peak. LRMS m/z (M^+): calcd, 628.30, found, 628.35.

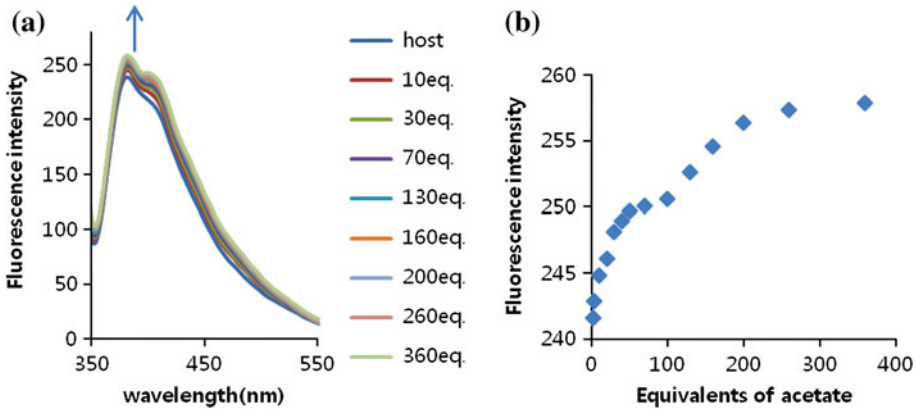


Fig. 1 The change of fluorescence spectra (**a**) and its saturation curve (**b**) in receptor **3** when tetrabutylammonium acetate was added

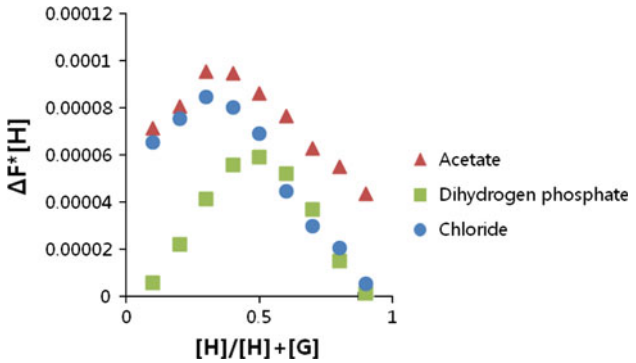


Fig. 2 The Job plots of **3** with tetrabutylammonium dihydrogen phosphate, tetrabutylammonium acetate, and tetrabutylammonium chloride using fluorescence spectroscopy

The complexation ability of receptor **3** for the acetate ion was also measured by standard ^{1}H NMR titration experiments in DMSO-d_6 using a constant host concentration (1 mM) and increasing concentrations of anions (2–9 equiv. Fig. 3). The addition of tetrabutylammonium acetate salt to the solution of 1 mM in DMSO-d_6 resulted in downfield shifts in both the amide N–H hydrogen and carbamate N–H hydrogen. The amide and carbamate peak in receptor **3** without acetate appeared at 8.98 and 6.97 ppm respectively in DMSO-d_6. Both amide and carbamate peaks moved to 9.10 and 7.04 ppm respectively after the addition of about 9 equivalents of acetate. No further shifts were observed. The possibility that anion binding took place on protonated quinoline nitrogen was eliminated. Protonated proton on the quinoline nitrogen usually appears in the range of chemical shift 12–16 ppm. However, any new proton peaks in this region were not observed during titration. Therefore, it was unlikely that nitrogens in the quinoline were protonated during titration. The shifts of N–H peaks in the amide and carbamate indicated that only amide and carbamate N–H hydrogens were major hydrogens involved in hydrogen bonding with anions during titration. Therefore, the chemical shifts of these hydrogens were analyzed by EQNMR [20]. The association constant ($\beta_2 = K_1K_2$) calculated from ^{1}H NMR titration gave 3.0×10^5 for acetate, which is similar value from the fluorescence titration.[2]

Like acetate, spherical shaped halide also bound to receptor **3** in a 1:2 host–guest stoichiometry (Fig. 2). In titration, almost same phenomena were observed with spherical halides. For example, chloride also showed two saturation points in fluorescence titration like acetate (Fig. 4). In ^{1}H NMR titration in DMSO-d_6, both amide and carbamate peaks moved to 9.02 and 6.98 ppm respectively after the addition of about 50 equivalents of chloride (Fig. 5). Association constant ($\beta_2 = K_1K_2$) for chloride was calculated as 8.0×10^4 from fluorescence titration and 8.0×10^4 from ^{1}H NMR titration. In the case of fluoride, deprotonation of both amide and carbamate N–H peaks were observed with addition of about 2 equivalents of fluoride ions (Fig. 6). The deprotonation of both amide and carbamate N–H peaks occurs due to strong basicity of fluoride. Fluoride interacts with receptor **3** mostly as base rather than mild anion guest. Therefore, association constants were not calculated. All association constants for the anions investigated were shown in Table 1. The complexation mode of chloride and carboxylate can be imagined easily. We suggest that the receptor **3** utilizes one amide N–H and one carbamate N–H to bind one anion. Therefore, it can bind two anions. However, its K_2 values were much smaller than those of K_1. This result suggests that the conformation of the receptor **3** was still cisoid while it bound to these anions.

Among the anions investigated only dihydrogen phosphate showed 1:1 stoichiometry. Almost same phenomena were observed with dihydrogen phosphate in titration. In fluorescence titration, the intensity of emission spectrum from 20 μM solution of the receptor **3** gradually increased as the concentration of tetrabutylammonium dihydrogen

[2] In the NMR titration and fluorescence titration, solution of anion was added to the solution of host. The volume change of host solution was less than 4 % during titration and dilution effect was ignored. In the NMR titrations the mole ratio was measured by integration values between host **3** and tetrabutylammonium anion salts.

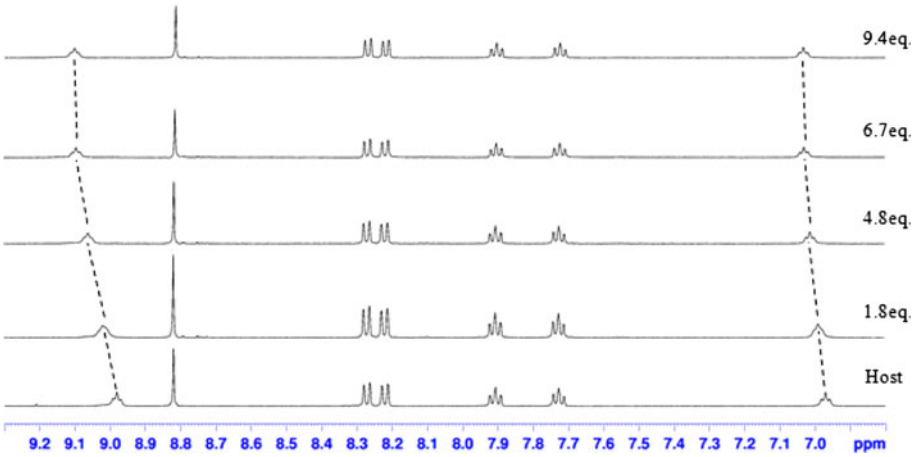


Fig. 3 ^{1}H NMR spectra of 1 mM of **3** with increased amounts of tetrabutylammonium acetate in DMSO-d_6. The shift of amide and carbamate N–H peaks are designated by *dotted lines*

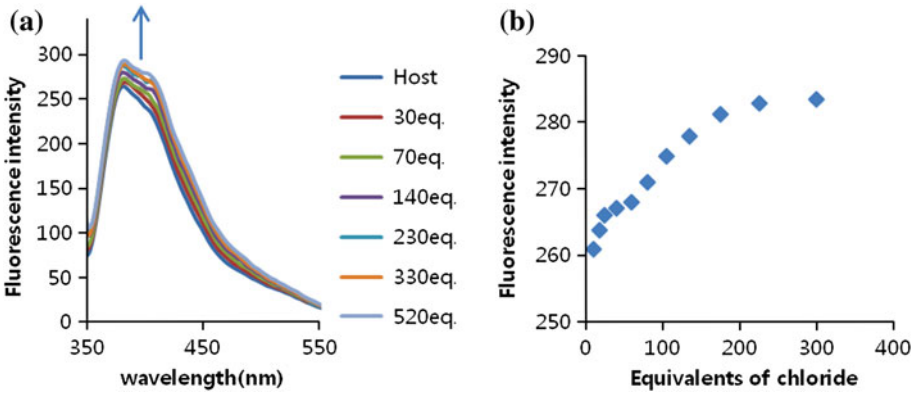


Fig. 4 The change of fluorescence spectra (**a**) and its saturation curves (**b**) in the receptor **3** when tetrabutylammonium chloride was added

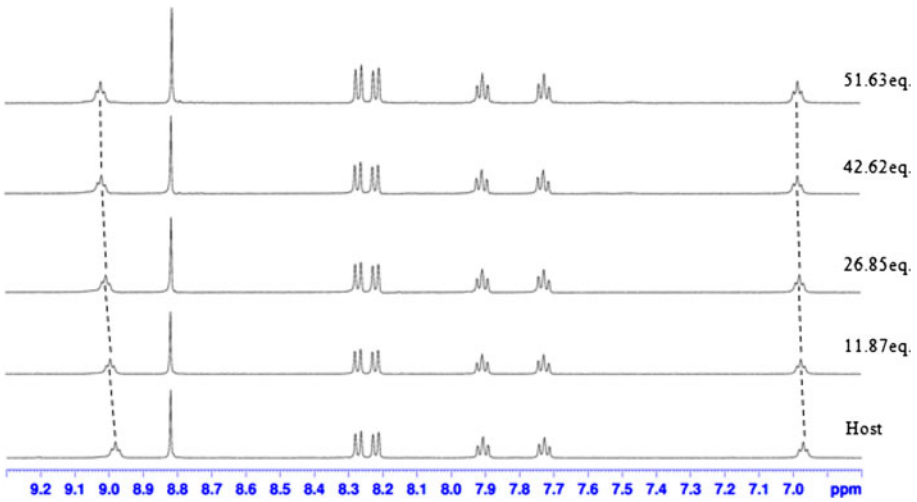


Fig. 5 ^{1}H NMR spectra of 1 mM of **3** with increased amounts of tetrabutylammonium chloride in DMSO-d_6. The shift of amide and carbamate N–H peaks are designated by *dotted lines*

phosphate salts was increased (4–600 equiv., Fig. 7a). In ^{1}H NMR titration, both amide and carbamate peaks moved until 9.14 and 7.04 ppm respectively with addition about 25 equivalent of dihydrogen phosphate (Fig. 7b). From fluorescence titration and ^{1}H NMR titration, the association constant was calculated as 4.9×10^{2} and 4.0×10^{2} respectively.

Although receptor **3** showed 1:1 binding stoichiometry for dihydrogen phosphate, its association constant was quite low compared with other anions. To understand the physical origin of this comparatively low binding energy, we performed computational modeling. We tried several possible geometries of host–guest complex. The potential energy surface upon bonding was very flat, and difficult

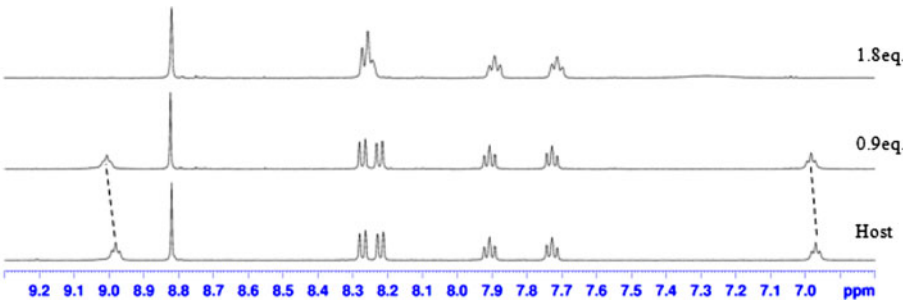


Fig. 6 ^{1}H NMR spectra of 1 mM of **3** with increased amounts of tetrabutyl-ammonium fluoride in DMSO-d_6. The shift of amide and carbamate N–H peaks are designated by *dotted lines*

Table 1 The association constants (M^{-1}) of the receptor **3** and various anions in DMSO

Anion	Fluorescence			NMR		
	K_1	K_2	$\beta_2 = K_1K_2$	K_1	K_2	$\beta_2 = K_1K_2$
$H_2PO_4^-$	4.9×10^2	–	–	4.0×10^2	–	–
Cl^-	8.6×10^3	9.3×10^0	8.0×10^4	3.8×10^3	2.1×10^1	8.0×10^4
$CH_3CO_2^-$	7.0×10^3	4.0×10^1	2.8×10^5	1.6×10^3	1.9×10^2	3.0×10^5
$C_6H_5CO_2^-$	1.3×10^3	1.0×10^2	1.3×10^5	5.1×10^3	2.4×10^1	1.2×10^5

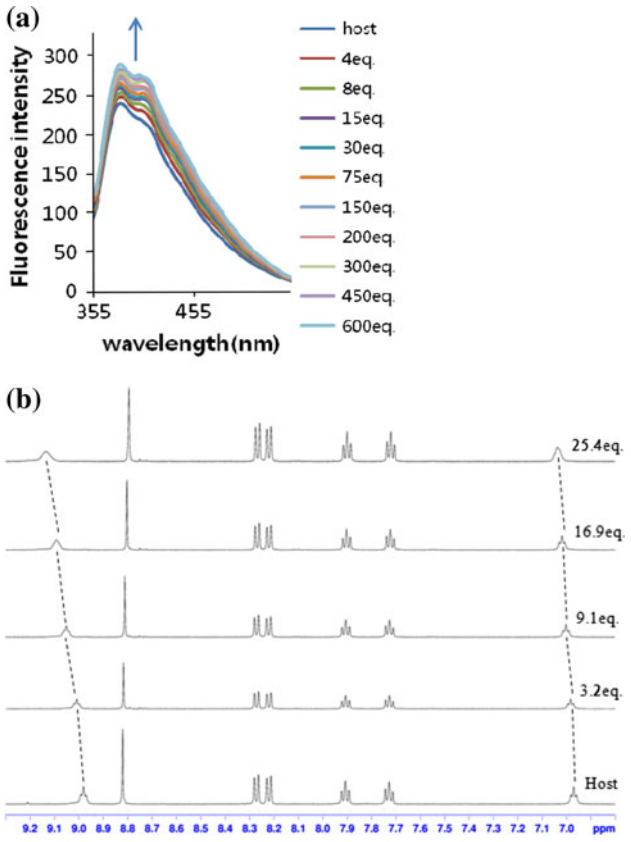


Fig. 7 The change of fluorescence spectra (**a**) and ^{1}H NMR titration spectra (**b**) of tetrabutylammonium dihydrogen phosphate in DMSO-d_6

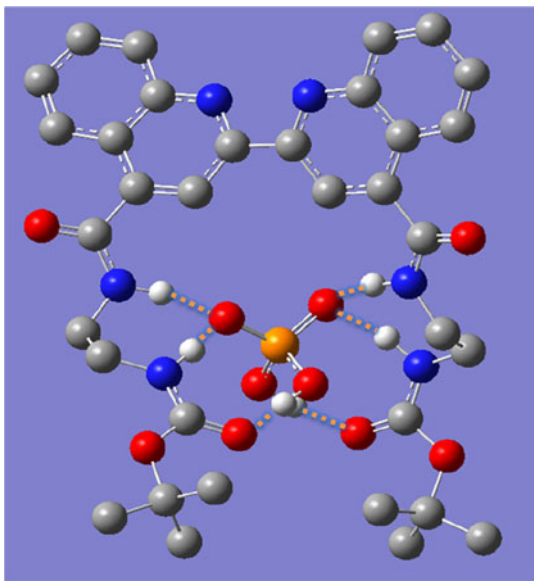


Fig. 8 The complex structure of **3** and dihydrogenphospate

to define exact local minima. To avoid too much computational time, we first used B3LYP/3-21G* method [21] for optimization. More reliable binding energy was obtained using B3LYP/6-31+G* level [21] of theory at the given level of geometry. The calculated gas phase binding energy is −41.2 kcal/mol which is quite low as observed in titration experiments. The most plausible structure is shown in Fig. 8. Basically this shows 6 hydrogen bonds. The distances between heavy atoms range 2.62–2.69 Å and the angle of hydrogen bondings span 153–177°. So, the six H-bondings are within the normal range of H-bonding. Even though the individual H-bondings are within normal hydrogen bonding range, the structure does not seem to fit well to match the host

binding pocket. Since the six H-bondings were interconnected, it was very difficult to point out why this structure does not fit very well. One possible explanation could involve the geometry of structure of guest molecule. This host molecule could prefer the planar structure rather than tetrahedral one.

Among the anions with same geometry, the association constants simply reflected basicities of anions. Association constants of benzoate was lower than that of acetate and weak basic spherical anions such as bromide and iodide did not have any affinity for receptor **3**. In addition, weak basic tetrahedral anions such as hydrogen sulfate and perchlorate did not show any affinity for receptor **3**.

In summary, we have designed and synthesized a new fluorescent receptor based on two amide hydrogens and two carbamate hydrogens anchored at 4,4′-position of biquinoline. Fluorescence and ^{1}H NMR titration showed that receptor **3** bound anions with different stoichiometry depending on the shape of anions and its association constants for anions reflected the basicities of anions. Trigonal planar carboxylates and spherical halides bound to the receptor **3** in 1 : 2 stoichiometry and tetrahedral dihydrogen phosphate the receptor **3** in 1:1 stoichiometry.

Acknowledgments This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2010-0021333).

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