Tetrahedron Letters 50 (2009) 807–810

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Selective anion recognition by retarding the cooperative polarization effect of amide linkages

Gang Woo Lee, Narinder Singh, Hee Jung Jung, Doo Ok Jang *

Department of Chemistry, Yonsei University, Wonju 220-710, Republic of Korea

ARTICLE INFO

Article history:
Received 9 October 2008
Revised 27 November 2008
Accepted 1 December 2008
Available online 6 December 2008

Keywords:
Chemosensor
Dihydrogen phosphate
Cooperative polarization
Benzthiazole
Fluorescent

ABSTRACT

A novel benzthiazole-based fluorescent receptor was synthesized, and its anion recognition properties were compared with those of similarly designed benzimidazole-based receptors. The selectivity of this receptor for the recognition of dihydrogen phosphate is enhanced by employing hydrogen bonding, in which cooperative polarization effect to the carbonyl group of amide linkages is lacking.

Development of chemosensors for the recognition and detection of anions is gaining attention as an important research area in modern supramolecular chemistry.[1] N–H bonds in ureas are employed in the design of receptors to ensure the anion binding affinity of the receptors.[2] To enhance the hydrogen bond donor ability of these receptors through NH bonds, designs of the receptors are incorporated with electron-withdrawing groups[3] and/or provided the cooperative polarization to the carbonyl group of the ureas.[4] Introducing electron-withdrawing groups often increases the acidities of the NH bonds to such an extent that the receptors act as H^+ donors to basic anions such as fluoride and acetate, resulting in deprotonation of the receptors. Hence, anions do not remain under the supramolecular control of the receptors.[5]

The cooperative polarization effect is observed in some biotic anion receptors such as a channel-like coiled structure with an array of glutamines forming a ring of cooperatively hydrogen-bonded amide links, which encapsulates a chloride ion.[6] This type of cooperative polarization is often observed in several biological systems.[7] The mechanisms employed by nature are often considered for the design of abiotic receptors. In this context, the concept of cooperative polarization has been incorporated to the design of some supramolecular receptors for better hydrogen bonding.[4,8]

Our previous work on the recognition behavior of receptor **2** had revealed that the C–H hanging from the aromatic platform into the cavity of receptor **2** and the N–H of receptor **2** act as strong binding sites for encapsulating anions (Scheme 1).[9] These binding sites are so proficient that receptor **2** binds with several anions, and consequently low selectivity is observed for a particular anion.[10] The hydrogen donor capacity of the N–H in receptor **2** is strengthened by the presence of $-NO_2$ group. These bonding interactions are further strengthened by cooperative polarization of the amide group, which is accomplished by coordinating the carbonyl to hydrogen donor of benzimidazole moiety as shown in Scheme 1.

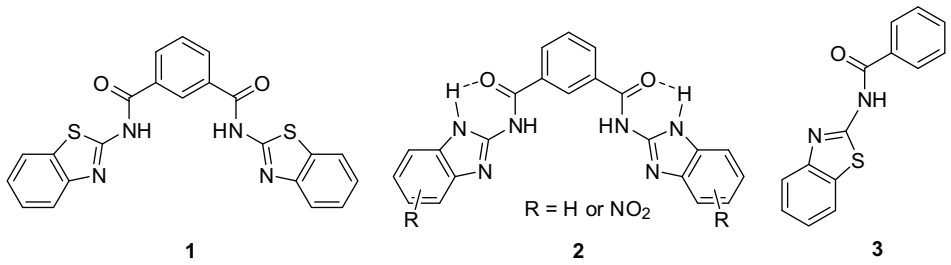
To improve the selectivity for dihydrogen phosphate upon fluoride and acetate, we designed and synthesized receptor **1**. The rationale behind the design of receptor **1** is based upon the fact that receptor **1** is devoid of many N–H donors, and the amide N–H has no chance of cooperative polarization. Therefore, in this design, the hydrogen bond donor aptitude of the receptor decreases, whereas the hydrogen bond acceptor capacity of the receptor is amplified by providing additional hydrogen bond acceptor sites.

Receptor **1** was synthesized and studied for its recognition behavior toward various anions. The results were compared with a control monopodal receptor **3**. Receptors **1**[11] and **3**[12] were synthesized by a reaction of 2-aminobenzthiazol with isophthaloyl dichloride and benzoyl chloride, respectively. A 10 μM concentration of receptor **1** upon excitation at 305 nm in CH_3CN/H_2O (99:1, v/v) exhibited a fluorescence spectrum with λ_{max} = 452 nm. The selectivity of receptor **1** toward various anions was examined by following the changes in fluorescence intensity of receptor **1** upon adding tetrabutylammonium salt of a particular anion. The results did not exhibit much improved selectivity for any anions.

We had previously observed in the ^1H NMR titration that DMSO competes with an anion for N–H binding sites of receptor **2**. Gale and co-workers have also reported a similar observation in the

* Corresponding author. Tel.: +82 337602261; fax: +82 337602182.
E-mail address: dojang@yonsei.ac.kr (D.O. Jang).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.12.003



Scheme 1.

crystal structure of a similar type of receptor design.[13] Based on these observations, we envisioned that if the solvent system contains a large amount of DMSO, the N–H donor capacity of the receptor might decrease. Hence, we studied the anion recognition properties of receptor **1** in CH_3CN/DMSO/water (98:1:1, v/v/v) HEPES buffer solution, in which a minimum amount of DMSO was used to dissolve receptor **1**. We took a 10 μM solution of receptor **1**, and then 300 μM solutions of a particular anion were added. The fluorescence spectrum was measured one-by-one after adding the solution of a particular anion. Figure 1 presents the comparison of fluorescence spectrum of the pure host with the spectra of solutions containing the host along with a particular anion. These data are presented in Figure 2. As we expected, the selectivity of receptor **1** for dihydrogen phosphate was dramatically improved in our tailored solvent combination. Moreover, hydrogen phosphate and phosphate have poor binding affinity for the coordination sphere of receptor. These results imply that the hydrogens of the H–O–P segment of dihydrogen phosphate bind first with the hydrogen bond acceptor sites of the benzthiazole moiety since DMSO cannot compete with an anion for these binding sites, and afterward a O═P segment interacts with hydrogen bond donor sites of the receptor. This point is cleared by the fact that in the present solvent system, receptor **1** has no affinity with other anions such as fluoride and acetate, indicating that the hydrogen bond donor sites are too weak to complex with any anions.

As a control experiment, the same solvent system was used to study the recognition properties of receptor **3**. In this typical experiment, we selected a 20 μM concentration of receptor **3**. This concentration of receptor **3** will provide approximately the same number of binding sites as one can expect from the 10 μM concentration of receptor **1**. Receptor **3** did not bind with any anions.

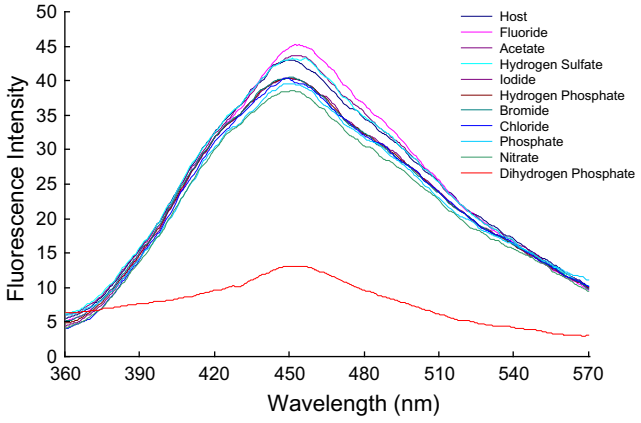


Figure 1. Changes in fluorescent intensity of receptor **1** (10 μM) upon addition of a particular tetrabutylammonium salt (300 μM) in CH_3CN/DMSO/H_2O (98:1:1, v/v/v) buffer solution (10 mM HEPES, pH = 6.7 ± 0.1) (λ_{ex} = 305 nm).

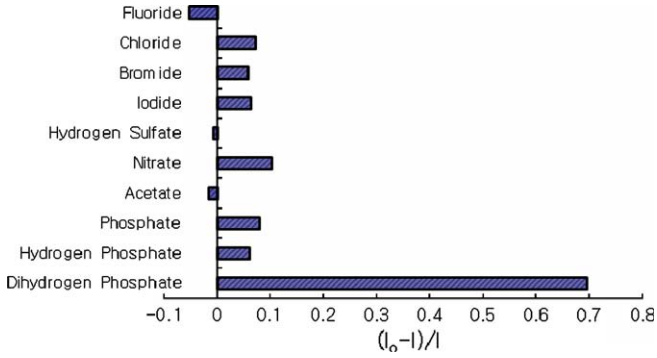


Figure 2. Changes in fluorescent ratio of receptor **1** (10 μM) at 452 nm upon addition of a particular tetrabutylammonium salt in CH_3CN/DMSO/H_2O (98:1:1, v/v/v) buffer solution (10 mM HEPES, pH = 6.7 ± 0.1) (λ_{ex} = 305 nm).

Thus, the control experiment revealed the importance of reasonable binding sites of receptor **1**. In other words, the availability of complementary binding sites in the design of receptor **1** ensured the authentic binding of dihydrogen phosphate.

To investigate the binding abilities of receptor **1** for dihydrogen phosphate, titration studies were performed (Fig. 3). The association constant was determined from decreases in fluorescence intensity of receptor **1** as the concentration of tetrabutylammo-

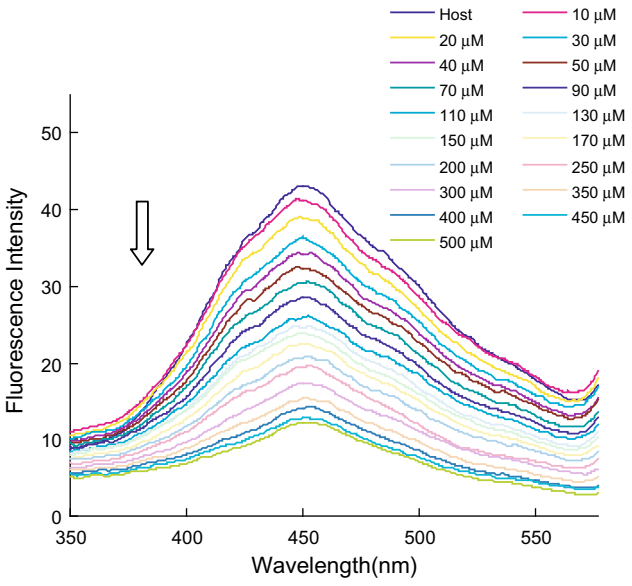


Figure 3. Changes in fluorescent spectra of receptor **1** (10 μM) upon successive addition of tetrabutylammonium dihydrogen phosphate (0–500 μM) in CH_3CN/DMSO/H_2O (98:1:1, v/v/v) buffer solution (10 mM HEPES, pH = 6.7 ± 0.1) (λ_{ex} = 305 nm).

nium dihydrogen phosphate increased. The association constant was calculated on the basis of Benesi–Hildebrand plot, and it turned out to be $(7.9 \pm 1.3) \times 10^3\ M^{-1}$ for dihydrogen phosphate.[14]

To determine the stoichiometric ratios of receptor **1** and dihydrogen phosphate, the continuous variation methods were used.[15] Figure 4 shows the Job plot of the fluorescence intensity of receptor **1**. The results illustrate that the receptor–guest complex concentration approaches a maximum when the molar fraction of receptor is about 0.5, which means that dihydrogen phosphate forms a 1:1 complex with receptor **1**.

The coordination sphere offered by receptor **1** for encapsulating dihydrogen phosphate was predicted with the MacroModel studies (Fig. 5).[16] These studies show that the pseudocavity of receptor **1** can provide the optimum binding sites for dihydrogen phosphate through N–H···O=P and N···H–OP hydrogen bond interactions. Though these studies are the modeling of interactions that prevail in the absence of competition from the solvents, they have provided a preliminary idea for the host–guest interactions.

The exact binding properties of receptor **1** toward dihydrogen phosphate were examined on the basis of ^{1}H NMR titration experiments. The successive addition of tetrabutylammonium salt of dihydrogen phosphate to a solution of receptor **1** resulted in marked shifts in ^{1}H NMR signals as shown in Figure 6. Interestingly, the C–H proton signal of aromatic platform that resonates at δ 8.91 ppm experienced a downfield shift by $\Delta\delta$ = 0.11 ppm after adding 1.0 equiv of dihydrogen phosphate. The broad NH signal of amide linkages also shifted downfield. During the course of titration, this signal broadened. Thus, we could not follow the shifts of this proton after adding 0.4 equiv of dihydrogen phosphate. Although this signal broadness limited us to point out the fate of NH proton at 1:1 mixture of the host and the guest, these concurrent shifts in the C–H and N–H proton signals led us to conclude

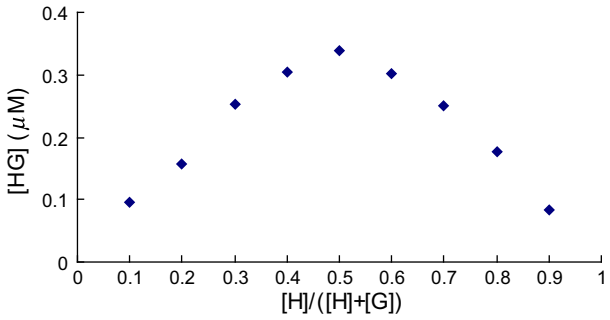


Figure 4. The Job plot showing 1:1 stoichiometry of the complex formed between receptor **1** and dihydrogen phosphate.

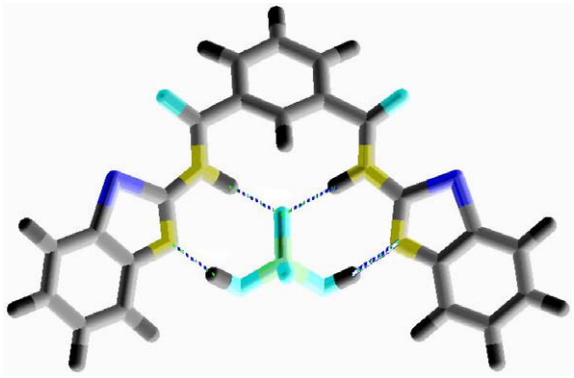


Figure 5. Receptor **1** exhibits the pseudocavity complementary to the steric requirements of dihydrogen phosphate.

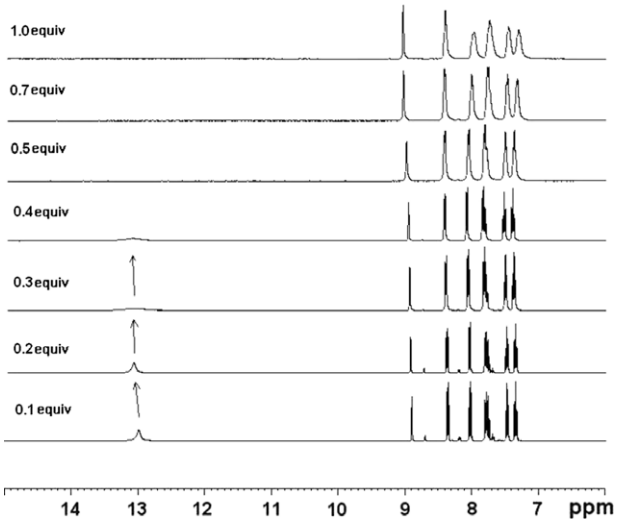


Figure 6. ^{1}HNMR spectra of receptor **1** (1 mM in DMSO-d_6) upon successive addition of tetrabutylammonium salt of dihydrogen phosphate.

that these two types of proton donor sites make a convergent array of hydrogen bonding for binding O=P of dihydrogen phosphate by means of a model of $(N–H)_2\cdots O(=P)\cdots H–C$. In addition, the aromatic signals of benzthiazole moiety shifted drastically, demonstrating the function of hydrogen bond acceptor sites of benzthiazole moiety. In short, the NMR titration experiments confirmed the binding mode proposed by the molecular modeling studies.

In conclusion, we developed a method to manage the selectivity of a receptor for a particular anion both by engineering the optimum binding sites in the receptor design and by modulating the solvent combination.

Acknowledgment

This work was supported by the Center of Bioactive Molecular Hybrids.

References and notes

1. (a) Yocum, C. F. *Coord. Chem. Rev.* **2008**, *252*, 296–305; (b) Lenthall, J. T.; Steed, J. W. *Coord. Chem. Rev.* **2007**, *251*, 1747–1760; (c) Gale, P. A. *Acc. Chem. Res.* **2006**, *39*, 465–475; (d) Yoon, J.; Kim, S. K.; Singh, N. J.; Kim, K. S. *Chem. Soc. Rev.* **2006**, *35*, 355–360; (e) Katayev, E. A.; Ustynyuk, Y. A.; Sessler, J. L. *Coord. Chem. Rev.* **2006**, *250*, 3004–3047; (f) Davis, A. P. *Coord. Chem. Rev.* **2006**, *250*, 2939–2951.
2. (a) Gunnlaugsson, T.; Glynn, M.; Tocci, G. M.; Kruger, P. E.; Pfeffer, F. M. *Coord. Chem. Rev.* **2006**, *250*, 3094–3117; (b) Evans, L. S.; Gale, P. A.; Light, M. E.; Quesada, R. *Chem. Commun.* **2006**, 965–967; (c) Wu, C.-Y.; Chen, M.-S.; Lin, C.-A.; Lin, S.-C.; Sun, S.-S. *Chem.-Eur. J.* **2006**, *12*, 2263–2269; (d) Quinlan, E.; Matthews, S. E.; Gunnlaugsson, T. *Tetrahedron Lett.* **2006**, *47*, 9333–9338; (e) Pfeffer, F. M.; Gunnlaugsson, T.; Jensen, P.; Kruger, P. E. *Org. Lett.* **2005**, *7*, 5357–5360; (f) Piatek, P.; Jurczak, J. *Chem. Commun.* **2002**, 2450–2451.
3. Suksai, C.; Tuntulani, T. *Chem. Soc. Rev.* **2003**, *32*, 192–202.
4. Hughes, M. P.; Smith, B. D. *J. Org. Chem.* **1997**, *62*, 4492–4499.
5. (a) Amendola, V.; Esteban-Gomez, D.; Fabbrizzi, L.; Licchelli, M. *Acc. Chem. Res.* **2006**, *39*, 343–353; (b) Esteban-Gomez, D.; Fabbrizzi, L.; Licchelli, M. *J. Org. Chem.* **2005**, *70*, 5717–5720.
6. Malashkevich, V.; Kammerer, R. A.; Efimov, V. P.; Schulthess, T.; Engel, J. *Science* **1996**, *274*, 761–765.
7. Jeffrey, G. A.; Saenger, W. *Hydrogen Bonding in Biological Structures*; Springer: Berlin, 1991.
8. Burrows, A. D.; Chan, C.-W.; Chowdhry, M. M.; McGrady, J. E.; Mingos, D. M. P. *Chem. Soc. Rev.* **1995**, *24*, 329–339.
9. Moon, K. S.; Singh, N.; Lee, G. W.; Jang, D. O. *Tetrahedron* **2007**, *63*, 9106–9111.
10. For examples of anion recognition in the order of basicity: (a) Bowman-James, K. *Inorg. Chem.* **2003**, *42*, 1397–1399; (b) Inoue, Y.; Kanbara, T.; Yamamoto, T. *Tetrahedron Lett.* **2003**, *44*, 5167–5169; (c) Hossain, A.; Kang, S. O.; Powell, D.; Stephen, D.; Arungundram, S. S.; Saunders, C. H. *Tetrahedron Lett.* **2002**, *43*, 7785–7788; (d) Coterón, J. M.; Kacket, F.; Schneider, H. J. *J. Org. Chem.* **1996**, *61*, 1429–1435; (e) Gale, P. A.; Sessler, J. L.; Král, V.; Lynch, V. *J. Am. Chem. Soc.* **1996**, *118*, 5140–5141.

11. *Synthesis of N,N′-di(benzo[d]thiazol-2-yl)isophthalamide* (**1**)*:* A solution of 2-aminobenzthiazole (1.55 g, 10.3 mmol) and isophthaloyl dichloride (1.0 g, 4.9 mmol) in pyridine was heated at 100 °C for 24 h. After cooling, the precipitation was washed with water, MeOH, and CH_2Cl_2 affording 0.24 g (82%) of compound **1** as a white solid. mp 302–303 °C; IR (KBr) 3408, 3061, 1679, 1538, 1453, 1275 cm^{-1}; ^1H NMR (DMSO-d_6) δ 13.03 (s, 2H, NH), 8.91 (s, 1H), 8.38 (d, 2H, J = 7.6 Hz), 8.06 (d, 2H, J = 7.6 Hz), 7.83–7.76 (m, 3H), 7.51 (t, J = 7.6 Hz, 2H), 7.39 (t, J = 7.6 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 165.5, 159.0, 148.0, 132.6, 132.3, 131.3, 129.2, 128.5, 126.2, 123.8, 121.8, 120.2. Anal. Calcd for $C_{22}H_{14}N_4O_2S_2$: C, 61.38; H, 3.28; N, 13.01; S, 14.90. Found: C, 60.99; H, 3.28; N, 13.01; S, 15.27.

12. (a) Angulo-Cornejo, J.; Lino-Pacheco, M.; Richter, R.; Hennig, L.; Hallmeier, K.-H.; Beyer, L. *Inorg. Chim. Acta* **2000**, *305*, 38–45; (b) Wang, J.; Peng, F.; Jiang, J.-I.; Lu, Z.-J.; Wang, L.-Y.; Bai, J.; Pan, Y. *Tetrahedron Lett.* **2008**, *49*, 467–470.
13. Fisher, M. G.; Gale, P. A.; Light, M. E. *New J. Chem.* **2007**, 1583–1584.
14. Benesi, H.; Hildebrand, H. *J. Am. Chem. Soc.* **1949**, *71*, 2703–2707.
15. Job, P. *Ann. Chim.* **1928**, *9*, 113–203.
16. Mohamedi, F.; Richards, N. G. T.; Liskamp, W. C. H.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comp. Chem.* **1990**, *11*, 440–467.