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Benzimidazole-based ratiometric fluorescent receptor for selective recognition of acetate

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Abstract—A novel fluorescent receptor bearing benzimidazole moieties as recognition sites was synthesized. The recognition behaviour of the receptor towards various anions has been evaluated in CH_3CN. The receptor showed ratiometric fluorescent changes only with CH_3COO^-, and it showed no significant response to any of other anions such as Cl^-, Br^-, I^-, HSO_4^-, NO_3^-, $C_6H_5COO^-$ and $H_2PO_4^-$.

Anions play a fundamental role in a wide range of chemical and biological processes. Acetate and dicarboxylates are critical components of numerous metabolic processes.[1] Acetate production and oxidation rate has been frequently used as an indicator of organic decomposition in marine sediments.[2] From industrial point of view, dicarboxylates are important not only as a raw material in the nylon industry but also for their use in manufacturing paper, cosmetics, plastics, dyes and paints.[3] The syntheses and studies of receptors for sensing various types of anions are interesting areas of current research.[4–13] During the last few years, much attention has been focused on the fluorescent sensing because of the high sensitivity and selectivity of this method.[14–25] Most of the reported receptors upon binding with anions exhibit fluorescence intensity changes on a single wavelength. However, several factors such as phototransformation, receptor concentration, and environmental effects contribute to the fluorescence intensity modulation of a system.[26] The ratiometric fluorescence signaling, which involves the measurement of changes in the ratio of the fluorescence intensities at two different wavelengths, is preferred to the conventional method of monitoring the fluorescence intensity at a single wavelength.[27,28] In comparison to the large number of ratiometric fluorophore receptors for sensing cations,[29–38] only a few examples are known for anion recognition.[39–44] The major challenge to ratiometric fluorescence signaling is developing a system with two emitting states having both the wavelength-dependent and substrate-dependent emission properties. To the best of our knowledge, there has been no report on benzimidazole-based ratiometric fluorescent receptor for the recognition of any anions. In our previous work, we have established that the 2-aminobenzimidazole-based receptors are efficient anion chemosensors.[45–47] Here we report the synthesis and recognition properties of a new benzimidazole-based ratiometric fluorescent receptor.

Receptor **2** was prepared by a series of steps as shown in Scheme 1.[48] For the synthesis of compound **1**, 2-aminobenzimidazole was heated to reflux with *p*-xylenedibromide along with NaH in DMF. Compound **1** was treated with ^{n}BuBr in DMF, and the bromide salt was exchanged with PF_6^-. The spectroscopic data were fully interpreted and found to be in accord with the formula of receptor **2**.

Upon excitation at 282 nm, receptor **2** exhibits emission at 443 nm in its fluorescence spectrum recorded with a 10 μM concentration in CH_3CN. To obtain a quantitative insight into the anion binding affinity of receptor **2**, the fluorescence intensity changes were measured upon the complexation of various anions. In these experiments 10 μM solutions of receptor **2** in CH_3CN were prepared along with a 20 μM concentration of a

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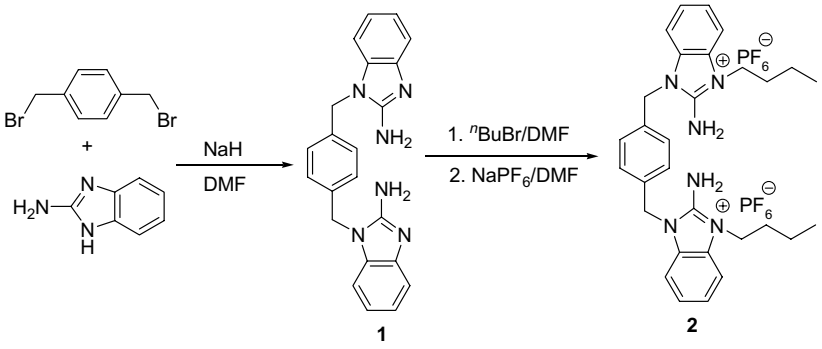

Scheme 1.

particular anion. In each experiment, the counter cation was tetrabutyl ammonium salt. The changes in fluorescent intensity of receptor **2** upon addition of a particular anion are shown in Figure 1, which shows that the maximum quenching in fluorescence intensity at 443 nm was observed with acetate, and also that a new band appeared at 339 nm. The anion induced fluorescence enhancement of receptor **2** may be a consequence of an increase in the 'molecular rigidification' or 'conformational restriction' of the receptor molecule upon the complexation of both amine groups of the receptor with acetate. According to this system, as a consequence of the guest coordination, the rigidity of the formed complex increases making the nonradiative decay from the excited state less probable; consequently, the emission intensity increases.[49–51] Since the receptor shows fluorescence quenching at 443 nm and fluorescence enhancement at 339 nm upon the binding of acetate anion, it can be used for the ratiometric sensing of acetate anion. The fluorescence ratiometric response of receptor **2** to selected anions is displayed in Figure 2. There were no such ratiometric changes in the fluorescence intensity of **2** upon addition of other anions such as Cl^-, Br^-, I^-, HSO_4^-, NO_3^-, $C_6H_5COO^-$ and $H_2PO_4^-$. This shows that receptor **2** is highly selective in its response to acetate in comparison to other anions. In a similar way, the cavity of **2** exhibits preferential binding of

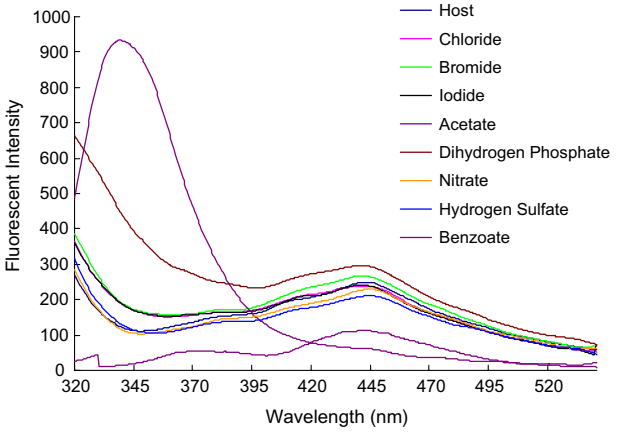

Figure 1. Changes in fluorescent intensity of receptor **2** (10 μM) upon addition of a particular anion salt in CH_3CN.

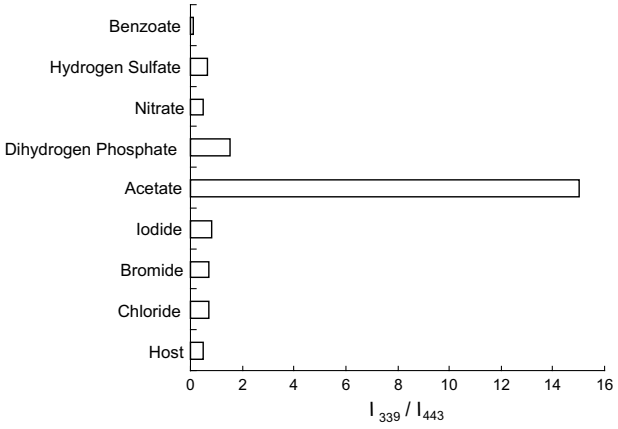

Figure 2. Fluorescence ratiometric response (I_{339}/I_{443}) of receptor **2** (10 μM) upon addition of a particular anion salt in CH_3CN.

AcO^- over $C_6H_5COO^-$. This can be explained by the steric features of the phenyl group in the binding site.

To find the association constant for the complex formed between receptor **2** and acetate anion, a titration was performed by taking a 10 μM solution of receptor **2** and increasing the amounts of anions (0–20 μM). After each addition of anion, the fluorescence intensity was measured. The titration results are shown in Figure 3 (Plot A). Similarly, a titration was performed to observe the changes in UV–vis spectrum of receptor **2**. Receptor **2** showed absorption bands at 276 and 282 nm in its UV–vis spectrum recorded with a 75 μM concentration in CH_3CN. Upon titration of receptor **2** with acetate, significant changes were observed in its UV–vis spectrum. By increasing the amount of acetate (0 to 225 μM) to the receptor solution, the absorption at 276 and 282 nm decreased, and a new band appeared at 302 nm whose intensity increased. This is attributed to electronic excitation through charge transfer chromophore. The excited state would be more stabilized by anion binding, resulting in a bathochromic shift in the absorption maxima.[11] These changes in UV–vis spectrum are shown in Figure 3 (Plot B).

From the changes in fluorescence and UV–vis spectrum, the association constant K_a of receptor **2** for acetate anion was calculated, on the basis of Benesi–Hildebrand

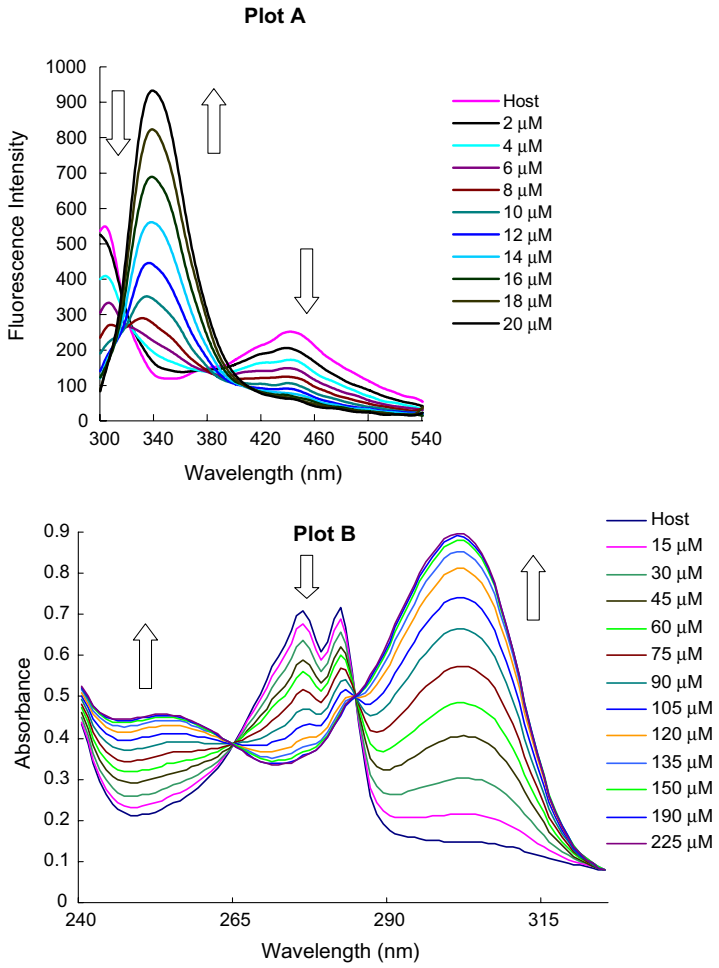

Figure 3. Changes in fluorescence spectrum of receptor **2** (10 μM) upon the addition of tetrabutylammonium acetate (0–20 μM) (Plot A) and changes in UV–vis spectrum of receptor **2** (75 μM) upon the addition of tetrabutylammonium acetate (0 to 225 μM) in CH_3CN (Plot B).

plot,[52] to be $(7.3\pm 0.6)\times 10^4\ M^{-1}$ and $(4.9\pm 0.1)\times 10^4\ M^{-1}$, respectively. Thus, receptor **2** can be used for selective recognition of acetate, and it can detect acetate as little as a low concentration of 2.0 μM.[53] The stoichiometry of the complex formed was determined by Job's plot,[54] and it was found to be 1:1 (Fig. 4).

To evaluate the role of basicity of binding anion, a titration was performed between receptor **2** (75 μM) and tetrabutylammonium hydroxide. The titration pattern was different from the one we obtained with acetate. This leads us to conclude that acetate binds through hydrogen bonding between N–H of the receptor and oxygen of acetate. In other words, we can say that the spectral changes of receptor **2** upon the addition of acetate are not a consequence of the basicity of acetate. The addition of water competes with acetate for hydrogen bonding with receptor **2**. From the changes in UV–vis spectrum, the association constant K_a of receptor **2** for acetate was calculated in CH_3CN/H_2O (9:1, v/v), and it was found to be $(1.9\pm 0.4)\times 10^3\ M^{-1}$. The low value of association constant under aqueous conditions shows that the hydrogen bondings between the receptor and the acetate are sensitive to the addition of water.

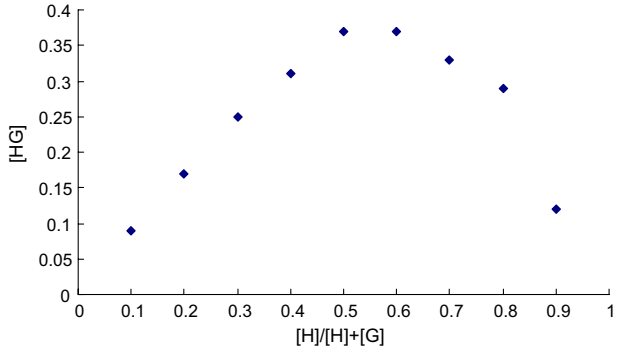

Figure 4. Job's plot of receptor **2** (10 μM) with acetate.

A ^1H NMR titration was performed to determine the responsible binding sites of receptor **2** for the recognition of acetate. The family of ^1H NMR spectra of receptor **2** upon the addition of 0.2–1.0 equiv of tetrabutylammonium acetate salt in CD_3CN is shown in Figure 5. Titration results showed that the aromatic protons of platform ring remained unchanged while the aromatic protons of benzimidazole shifted upfield by 0.5 ppm. The benzylic $-CH_2$ and $-CH_2$ of butyl flag were shifted

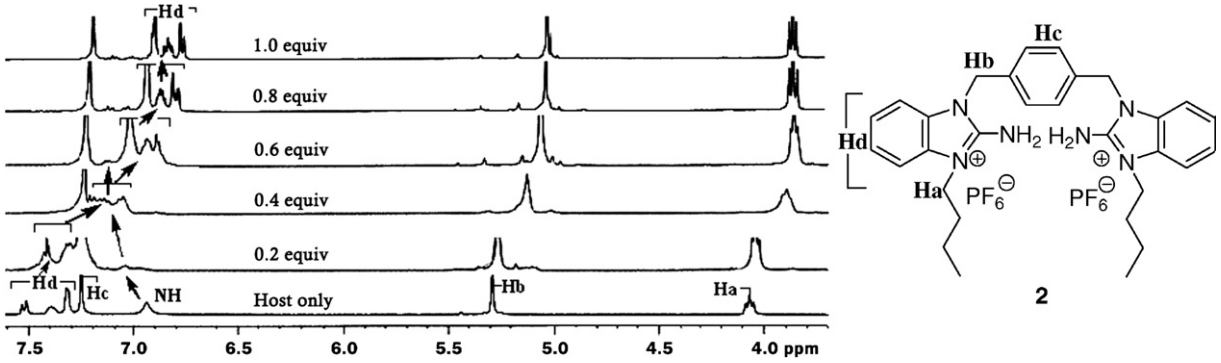

Figure 5. Family of ^{1}H NMR spectrum of the titration of receptor **2** with acetate (0–1.0 equiv) in CD_3CN.

by 0.3 and 0.2 ppm, respectively. The signal for NH_2 protons shifted downfield by 0.2 ppm. This NH signal was clear in the ^{1}H NMR titration when acetate was added up to 0.6 equiv. The signal disappeared during the course of titration owing to the broadening of the signal. The downfield shift in the NH signals indicates the formation of authentic hydrogen bonds between the host and the anion. This ruled out the possibility of anion induced deprotonation of the receptor.[55] These significant changes on the spectrum led us to conclude that the binding sites lying on the benzimidazole ring are responsible for the recognition of acetate anion.

In conclusion, we synthesized an easy-to-make fluoro-receptor based upon benzimidazole moieties, and its binding properties towards various anions were characterized. The receptor showed ratiometric fluorescent changes only with CH_3COO^- over a wide range of anions.

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Supplementary data

Supplementary data (spectroscopic measurements) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.10.060.

References and notes

1. Voet, D.; Voet, J. G. *Biochemistry*, 2nd ed.; Wiley: New York, 1995.
2. Ho, T.-Y.; Scranton, M. I.; Taylor, G. T.; Varela, R.; Thunell, R. C.; Muller-Karger, F. *Limnol. Oceanogr.* **2002**, *47*, 1119.
3. Carvalho, S.; Delgado, R.; Fonseca, N.; Felix, V. *New J. Chem.* **2006**, *30*, 247.
4. Gale, P. A. *Acc. Chem. Res.* **2006**, *39*, 465.
5. Katayev, E. A.; Ustynyuk, Y. A.; Sessler, J. L. *Coord. Chem. Rev.* **2006**, *250*, 3004.
6. Davis, A. P. *Coord. Chem. Rev.* **2006**, *250*, 2939.
7. Schmidtchen, F. P. *Coord. Chem. Rev.* **2006**, *250*, 2918.
8. Yoon, J.; Kim, S. K.; Singh, N. J.; Kim, K. S. *Chem. Soc. Rev.* **2006**, *35*, 355.
9. Bowman-James, K. *Acc. Chem. Res.* **2005**, *38*, 671.
10. Martínez-Máñez, R.; Sancenón, F. *Chem. Rev.* **2003**, *103*, 4419.
11. Suksai, C.; Tuntulani, T. *Chem. Soc. Rev.* **2003**, *32*, 192.
12. Sessler, J. L.; Camiolo, S.; Gale, P. A. *Coord. Chem. Rev.* **2003**, *240*, 17.
13. Gale, P. A. *Coord. Chem. Rev.* **2003**, *240*, 167.
14. Ojida, A.; Nonaka, H.; Miyahara, Y.; Tamaru, S.-I.; Sada, K.; Hamachi, I. *Angew. Chem., Int. Ed.* **2006**, *45*, 5518.
15. Wu, F.-Y.; Li, Z.; Guo, L.; Wang, X.; Lin, M.-H.; Zhao, Y.-F.; Jiang, Y.-B. *Org. Biomol. Chem.* **2006**, *4*, 624.
16. Liu, S.-Y.; Fang, L.; He, Y.-B.; Chan, W.-H.; Yeung, K.-T.; Cheng, Y.-K.; Yang, R.-H. *Org. Lett.* **2005**, *7*, 5825.
17. Liu, Z.-Q.; Shi, M.; Li, F.-Y.; Fang, Q.; Chen, Z.-H.; Yi, T.; Huang, C. H. *Org. Lett.* **2005**, *7*, 5481.
18. Kubo, Y.; Kobayashi, A.; Ishida, T.; Misawa, Y.; James, T. D. *Chem. Commun.* **2005**, *22*, 2846.
19. Cho, H. K.; Lee, D. H.; Hong, J.-I. *Chem. Commun.* **2005**, *13*, 1690.
20. Descaizo, A. B.; Rurack, K.; Weisshoff, H.; Martínez-Máñez, R.; Marcos, M. D.; Amoros, P.; Hoffmann, K.; Soto, J. *J. Am. Chem. Soc.* **2005**, *127*, 184.
21. Aoki, S.; Kagata, D.; Shiro, M.; Takeda, K.; Kimura, E. *J. Am. Chem. Soc.* **2004**, *126*, 13377.
22. Lee, D. H.; Kim, S. Y.; Hong, J.-I. *Angew. Chem., Int. Ed.* **2004**, *43*, 4777.
23. Boiocchi, M.; Bonizzoni, M.; Fabbrizzi, L.; Piovani, G.; Taglietti, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3847.
24. Wallace, K. J.; Belcher, W. J.; Turner, D. R.; Syed, K. F.; Steed, J. W. *J. Am. Chem. Soc.* **2003**, *125*, 9699.
25. Mizukami, S.; Nagano, T.; Urano, Y.; Odani, A.; Kikuchi, K. *J. Am. Chem. Soc.* **2002**, *124*, 3920.
26. Lakowicz, J. R. In *Topics in Fluorescence Spectroscopy*; Plenum Press: New York, 1994; Vol. 4.
27. Grynkiewicz, G.; Poenie, M.; Tsien, R. Y. *J. Biol. Chem.* **1985**, *260*, 3440.
28. Banthia, S.; Samanta, A. *J. Phys. Chem. B* **2006**, *110*, 6437.
29. Kim, J. S.; Choi, M. G.; Song, K. C.; No, K. T.; Ahn, S.; Chang, S.-K. *Org. Lett.* **2007**, *9*, 1129.
30. Peng, X.; Du, J.; Fan, J.; Wang, J.; Wu, Y.; Zhao, J.; Sun, S.; Xu, T. *J. Am. Chem. Soc.* **2007**, *129*, 1500.
31. Wang, J.; Qian, X.; Cui, J. *J. Org. Chem.* **2006**, *71*, 4308.
32. Coskun, A.; Akkaya, E. U. *J. Am. Chem. Soc.* **2006**, *128*, 14474.
33. Wu, Z.; Zhang, Y.; Ma, J. S.; Yang, G. *Inorg. Chem.* **2006**, *45*, 3140.
34. Royzen, M.; Dai, Z.; Canary, J. W. *J. Am. Chem. Soc.* **2005**, *127*, 1612.

35. Ajayaghosh, A.; Carol, P.; Sreejith, S. *J. Am. Chem. Soc.* **2005**, *127*, 14962.
36. Baruah, M.; Qin, W.; Vallee, R. A. L.; Beljonne, D.; Rohand, T.; Dehaen, W.; Boens, N. *Org. Lett.* **2005**, *7*, 4377.
37. Yang, R.-H.; Chan, W.-H.; Lee, A. W. M.; Xia, P.-F.; Zhang, H.-K.; Li, K. A. *J. Am. Chem. Soc.* **2003**, *12*, 2884.
38. Woodroofe, C. C.; Lippard, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 11458.
39. Wu, Y.; Peng, X.; Fan, J.; Gao, S.; Tian, M.; Zhao, J.; Sun, S. *J. Org. Chem.* **2007**, *72*, 62.
40. Chen, C.-L.; Chen, Y.-H.; Chen, C.-Y.; Sun, S.-S. *Org. Lett.* **2006**, *8*, 5053.
41. Oton, F.; Tarraga, A.; Molina, P. *Org. Lett.* **2006**, *8*, 2107.
42. Ojida, A.; Miyahara, Y.; Wongkongkatep, J.; Tamaru, S.-I.; Sada, K.; Hamachi, I. *Chem. Asian J.* **2006**, *1*, 555.
43. Kubo, Y.; Yamamoto, M.; Ikeda, M.; Takeuchi, M.; Shinkai, S.; Yamaguchi, S.; Tamao, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 2036.
44. Yann, B.; Martin, J. C.; David, P.; Rachel, S. *Chem. Commun.* **2002**, 1930.
45. Singh, N.; Jang, D. O. *Org. Lett.* **2007**, *9*, 1991.
46. Kim, H. S.; Moon, K. S.; Jang, D. O. *Supramol. Chem.* **2006**, *18*, 97.
47. Kang, J.; Kim, H. S.; Jang, D. O. *Tetrahedron Lett.* **2005**, *46*, 6079.
48. *Synthesis of compound* **1**: A solution of 2-aminobenzimidazole (500 mg, 3.76 mmol), α,α′-dibromo-*p*-xylene (496.3 mg, 1.88 mmol) and NaH (150.4 mg, 3.76 mmol) in DMF was heated to reflux for 48 h. Upon completion of reaction, the reaction mixture was added to cold water, and then solid was separated out. The solid material was washed with CH_2Cl_2 (50 mL) and ether (50 mL) affording the compound **1** (429 mg, 62%); mp 318–319 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.20 (s, 4H, Ar), 6.51 (s, 4H, NH_2), 6.80 (t, 2H, Ar, $J = 7.6$ Hz), 6.92 (t, 2H, Ar, $J = 7.6$ Hz), 7.00 (d, 2H, Ar, $J = 8.0$ Hz), 7.13 (m, 6H, Ar); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 44.8, 108.3, 115.2, 118.6, 120.9, 127.6, 134.5, 136.7, 143.2, 155.4; HRMS (FAB): calcd for $C_{22}H_{21}N_6$ ($M+H^+$) 369.1828; found, 369.1828. *Synthesis of receptor* **2**: A solution of compound **1** (368 mg, 1.0 mmol) and 1-bromobutane (400 mg, 2.9 mmol) in DMF was heated to reflux for 48 h under argon. Upon completion of the reaction, the reaction mixture was cooled to room temperature, and then solid was separated out. The solid material was washed with CH_2Cl_2 (50 mL) and ether (50 mL). The solid compound was again dissolved in hot DMF along with $NaPF_6$ (840 mg, 5.0 mmol), and was heated for 48 h under argon. The reaction mixture was poured into water. Solid material was separated out, and this material was washed several times with water and ether. Recrystallization from CH_2Cl_2 gave the product (540 mg, 70%); mp 250–252 °C; ^{1}H NMR (400 MHz, CD_3CN) δ 7.53 (d, 2H, Ar), 7.41–7.42 (m, 2H, Ar), 7.27–7.34 (m, 8H, Ar), 6.96 (s, 4H, NH), 5.32 (s, 4H, CH_2), 4.10 (t, 4H, CH_2), 1.76–1.80 (m, 4H, CH_2), 1.41–1.47 (m, 4H, CH_2), 0.98 (t, 6H, CH_2, $J = 8.0$ Hz); ^{13}C NMR (CD_3CN) δ 150.1, 135.3, 130.5, 129.9, 128.1, 124.6, 124.1, 111.2, 45.9, 43.3, 30.3, 19.8, 14.4; IR (KBr) 3434, 3232 cm^{-1}; HRMS (FAB): calcd for $C_{30}H_{38}F_{12}N_6P_2$ (M^+) 772.2442; found, 772.2425.
49. McFarland, S. A.; Finney, N. S. *J. Am. Chem. Soc.* **2002**, *124*, 1178.
50. Kondo, S.-I.; Kinjo, T.; Yano, Y. *Tetrahedron Lett.* **2005**, *46*, 3183.
51. Kondo, S.-I.; Sato, M. *Tetrahedron* **2006**, *62*, 4844.
52. Benesi, H.; Hildebrand, H. *J. Am. Chem. Soc.* **1949**, *71*, 2703.
53. Shortreed, M.; Kopelman, R.; Kuhn, M.; Hoyland, B. *Anal. Chem.* **1996**, *68*, 1414.
54. Job, P. *Ann. Chim.* **1928**, *9*, 113.
55. Amendola, V.; Boiocchi, M.; Fabbrizzi, L.; Palchetti, A. *Chem. Eur. J.* **2005**, *11*, 120.