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p-tert-Butylcalix[4]arene-based fluororeceptor for the recognition of dicarboxylates

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Abstract

p-tert-Butylcalix[4]arene-based dipodal receptor has been synthesized in cone conformation. The binding affinity of this receptor was evaluated with some aliphatic diacetates such as malonate, succinate, glutarate, adipate, pimelate, and suberate in CH_3CN. The receptor has the highest binding affinity for pimelate by making a 1:1 complex. This receptor was used to estimate pimelate in the presence of other dicarboxylates.

Keywords: Fluororeceptor; Calix[4]arene; Benzimidazole; Dicarboxylates

1. Introduction

Anions play a fundamental role in a wide range of biological, chemical, medical, and environmental processes. Thus, there is an ever-increasing interest in designing a host system that can recognize and sense anions.[1] Dicarboxylates are critical components of numerous metabolic processes including citric acid, glyoxylate cycles, and they play an important role in the generation of high energy phosphate bonds.[2] Dicarboxylates are also important from industrial point of view.[3] Numerous studies have been devoted to the design and synthesis of receptors as sensing probes for dicarboxylates. The dicarboxylates with a larger spacer length are difficult to encapsulate because they exhibit a variety of structures and conformations.[4] Consequently, in designing a receptor for long chain dicarboxylates the following aspects must be taken into account: the receptor–substrate binding site complementarities, the number of binding sites forming the binding subunits, and the distance separating the two sites from each other within the binding subunit.[5] In the present investigation, these points are achieved by providing benzimidazole motif as a suitable binding site in the design of calix[4]arene-based dipodal receptor. To date, there has been no report in which calix[4]arene-based receptor employs benzimidazole unit for the recognition of any anions, although we have proven in our previous work that the NH groups of 2-aminobenzimidazole can be efficient binding sites for recognizing anions.[6]

2. Results and discussion

Calix[4]arene-based dipodal receptor **2** was synthesized as shown in Scheme 1. The calix[4]arene-based dipodal aldehyde **1** was prepared by the literature method.[7] The final receptor **2** was prepared in good yield by the reaction of dipodal aldehyde **1** with 2-aminobenzimidazole and a subsequent reduction of imine linkages with $NaBH_4$. The conformation of receptor **2** was derived from the signals of the bridging methylene protons in ^1H NMR.[8] A pair of doublets with J=12.8 Hz in ^1H NMR and a signal at 31.7 ppm for $ArCH_2Ar$ in ^{13}C NMR show that the calix[4]arene exists in a cone conformation. The $-CH_3$ protons of *tert*-butyl groups appeared as two sharp singlets.

Receptor **2** displayed a maximum at 465 nm in its fluorescence spectrum that was recorded with its 10 μM concentration

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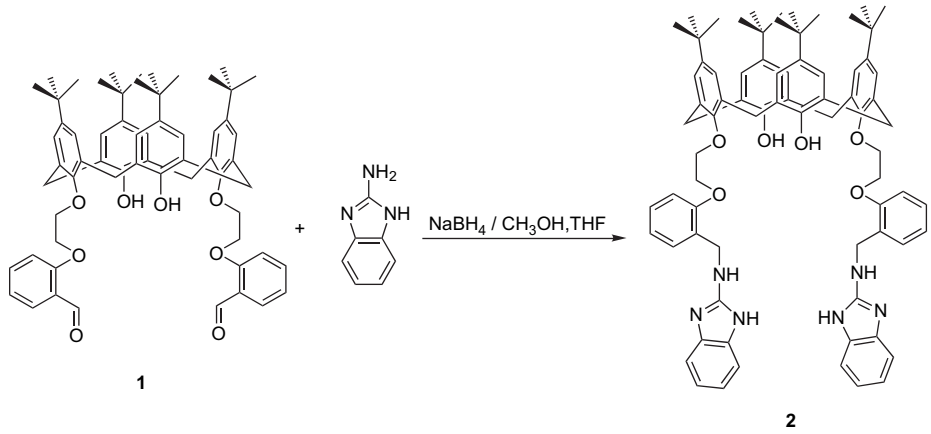


Scheme 1.

in CH_3CN when excited at 335 nm. The changes in fluorescence intensity of **2** upon addition of a particular anion are shown in Figure 1, and the fluorescence ratio $(I_0-I)/I_0$ is displayed in Figure 2.

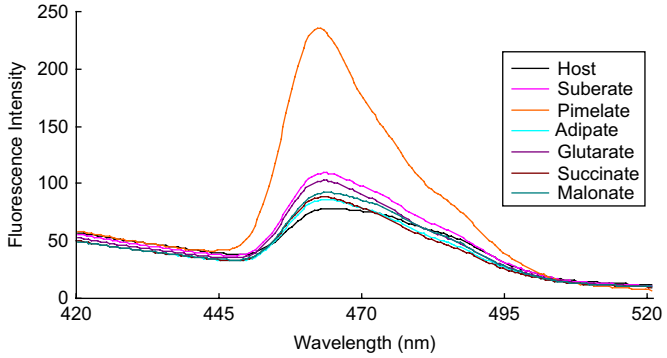


Figure 1. Changes in fluorescence intensity of **2** (10 μM) upon addition of 20 μM of a particular tetrabutylammonium anion salt in CH_3CN with excitation at 335 nm.

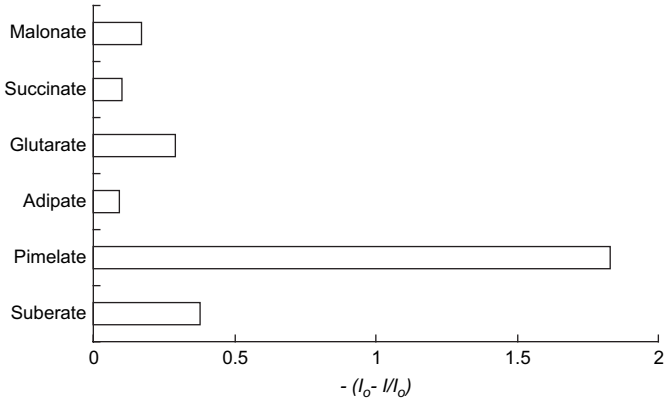
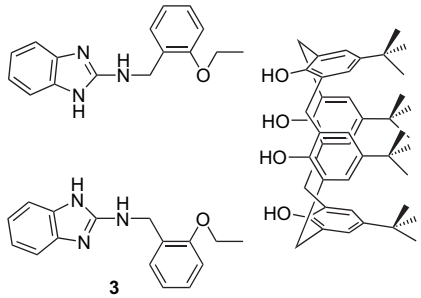


Figure 2. Fluorescence ratio (I_0-I/I_0) of **2** (10 μM) at 465 nm upon addition of 20 μM of a particular tetrabutylammonium anion salt in CH_3CN.

As can be seen in Figures 1 and 2, it is clear that there was a marked change in fluorescence intensity upon addition of pimelate, and no such significant change was observed upon addition of any other aliphatic diacetates such as malonate, succinate, glutarate, adipate, and suberate. The anion-induced fluorescence enhancement of receptor **2** may be due to the rigidity of complex formed between the host and the guest. In a rigid system, the probability of non-radiative decay is lesser. As a result, the emission intensity increases. The concept has been developed for the recognition of cations, anions, and sugars.[9] The preference for pimelate suggests that the flexible pods in **2** are more compatible to the chain length of pimelate than to any other dicarboxylates. To verify our point, we designed another compound (compound **3** in Scheme 2), which resembles the single pod of receptor **2**. We selected a 20 μM concentration of compound **3** along with 10 μM concentration of calix[4]arene (a 20 μM concentration of **3** along with 10 μM concentration of calix[4]arene has approximately the same number of binding sites as that of a 10 μM concentration of **2**), and then studied the changes in fluorescence intensity of **3** upon addition of pimelate. No significant changes in the fluorescence intensity were observed in the typical experiment. This proves that although **2** and **3** have the same type of binding sites, only an appropriate size of the pseudocavity of **2** can bind pimelate. Pimelate is believed to be bound cooperatively in the cavity.



Scheme 2.

To evaluate more about the properties of **2** as a receptor for pimelate, a fluorescence titration was carried out. The changes in fluorescence intensity of a 10 μM solution of **2** upon addition of tetrabutylammonium pimelate salt is shown in Figure 3. Upon addition of 1.0 equiv of pimelate anion to the solution of

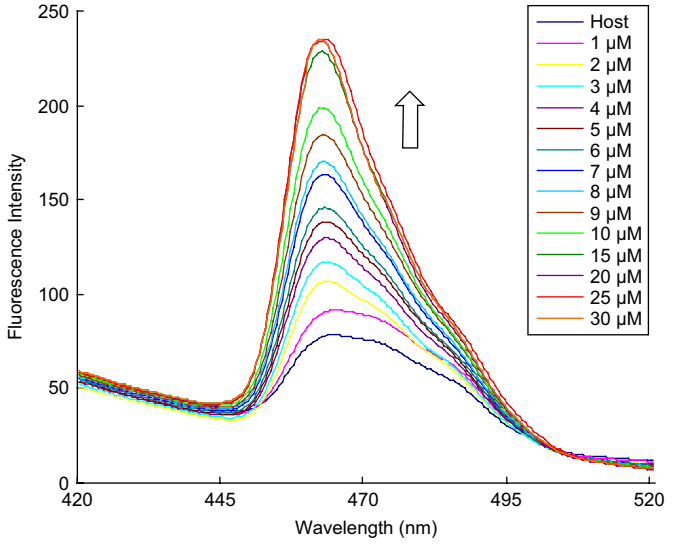


Figure 3. Fluorescence spectra changes of receptor **2** (10 μM) upon addition of tetrabutylammonium pimelate (0–30 μM) in CH_3CN.

receptor **2**, remarkable fluorescence enhancement was achieved, indicating the strong complexation that took place between **2** and pimelate.

Continuous variation methods were used to determine the stoichiometric ratios of the receptor and anionic guest molecules.[10] Figure 4 shows Job's plots of the fluorescence intensity of free receptor **2** and the intensity of the system with the molar fraction of the host {[H]/([H]+[G])} for a series of solutions in which the total concentration of host and dicarboxylate guest was constant, with the molar fraction of host continuously varying. The results illustrate that in case of pimelate and suberate, receptor–guest complex concentration approaches a maximum when the molar fraction of host is about 0.5, meaning that both the anions form 1:1 complex with the receptor. But malonate, succinate, glutarate, and adipate show the 1:2 mode of binding. This shows that these dicarboxylates are too short to bridge the binding sites, and thus they bind in a non-cooperative fashion. This was also evident from the small change in fluorescence intensity of receptor **2** upon addition of the dicarboxylates (Fig. 1).

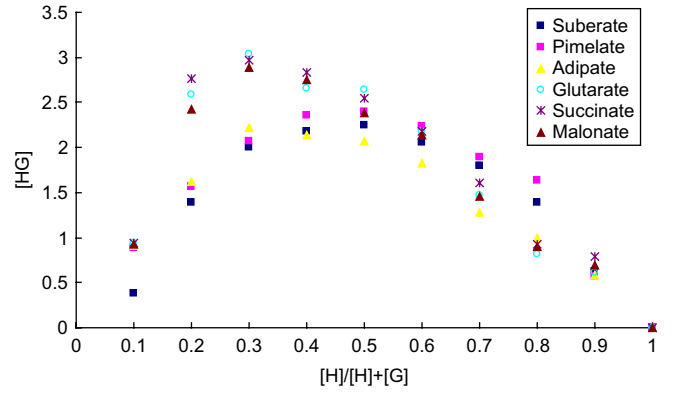


Figure 4. Job's plot between receptor **2** and dicarboxylates. The concentration of [HG] was calculated by the equation $[HG]=\Delta I/I_0\times[H]$.

Table 1
Binding constants and stoichiometries of dicarboxylates with receptor **2**

Dicarboxylate	Stoichiometry[a]	Binding constant[b]
Malonate	1:2	$(1.2\pm0.1)\times10^3$ M^{-2}
Succinate	1:2	$(2.5\pm0.1)\times10^3$ M^{-2}
Glutarate	1:2	$(1.3\pm0.1)\times10^4$ M^{-2}
Adipate	1:2	$(2.5\pm0.05)\times10^2$ M^{-2}
Pimelate	1:1	$(7.2\pm0.13)\times10^5$ M^{-1}
Suberate	1:1	$(3.3\pm0.06)\times10^5$ M^{-1}

[a] Stoichiometry of a complex formed between a particular dicarboxylate and receptor **2** was determined by Job's plot method.
[b] Binding constants were determined by literature methods.

The binding constants and stoichiometries of a particular dicarboxylate complex with receptor **2** are shown in Table 1. Results show that the binding ability of receptor **2** is best for pimelate. This may be due to the complementary of pimelate chain length with the distance between two binding sites of the receptor.

Based on the attentive analysis of binding strengths and stoichiometries of various complex formed, we proposed the binding mode for the dicarboxylates binding as shown in Figure 5. The 1:1 stoichiometries for pimelate and suberate indicate that they may bind in modes **A** or **B** rather than **C**.

The exact binding mode was established by comparing the ^{1}H NMR spectrum of pure receptor **2** with the ^{1}H NMR spectrum of the host mixed with 1.0 equiv of pimelate. ^{1}H NMR spectra of receptor **2** upon addition of tetrabutylammonium pimelate in $CDCl_3$ are shown in Figure 6. Upon addition of 1.0 equiv of pimelate salt, the signal of N–H at 10.45 ppm shifted to 10.71 ppm, and the other N–H signal at 8.14 ppm also shifted to 8.26 ppm. The OH signal of calixarene unit at 8.73 ppm was shifted to 8.85 ppm. These downfield shifts in signals indicate the formation of genuine hydrogen bonds between the host and the anion. This also ruled out the possibility of anion-induced deprotonation of the receptor.[12] These concurrent shifts in NH protons and OH protons of calixarene unit confirm that the binding mode for the encapsulation of pimelate is **A** instead of **B** (Fig. 5).

Experiments were designed to estimate pimelate in the presence of other dicarboxylates. In these typical experiments, fluorescence intensity was measured in a series of solutions containing receptor **2**, different amounts of pimelate, and other dicarboxylate having a concentration five times greater than the concentration of pimelate in CH_3CN (Fig. 7).

The fluorescence intensity was almost identical to that obtained in the absence of any of malonate, succinate, glutarate, adipate or suberate. This shows that receptor **2** is highly selective to pimelate in its response in comparison to other dicarboxylates. Thus, receptor **2** can be used for the selective recognition of pimelate, and it can detect pimelate up to a low concentration of 1 μM.[13]

3. Conclusions

We synthesized an easy-to-make neutral *p-tert*-butylcalix[4]arene-based dipodal fluororeceptor **2** based upon benzimidazole moieties, and investigated its binding properties

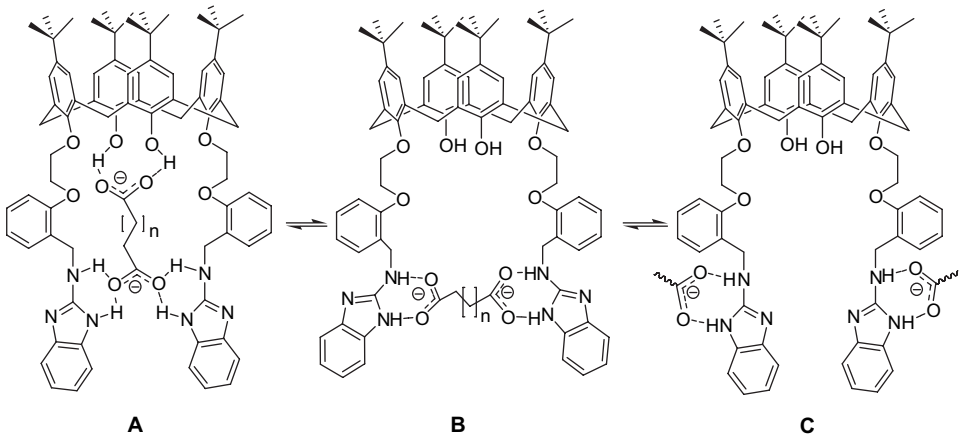


Figure 5. Possible modes of recognition of dicarboxylates in the pseudocavity of receptor **2**.

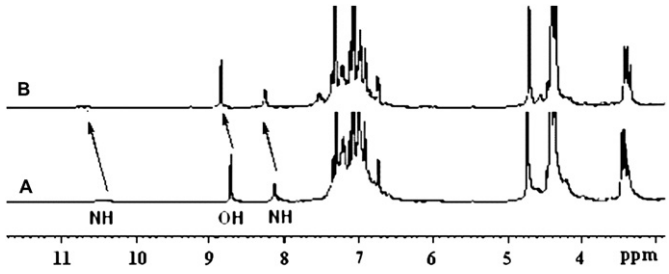


Figure 6. ^{1}H NMR spectra of (**A**) receptor **2** only and (**B**) receptor **2** and tetrabutylammonium pimelate ([G]/[H]=1).

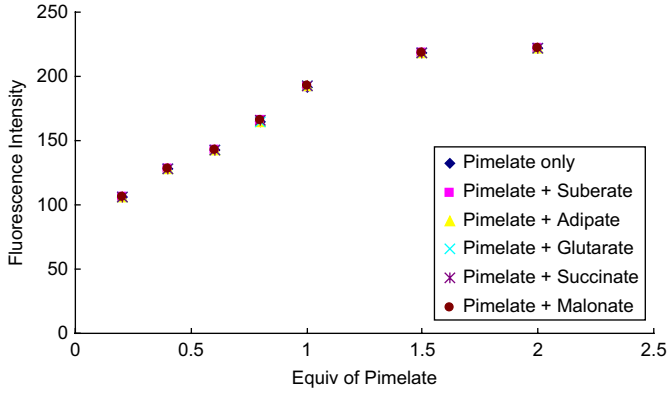


Figure 7. Estimation of pimelate in the presence of other dicarboxylates in CH_3CN.

toward dicarboxylates. It showed high selectivity for pimelate over a wide range of dicarboxylates.

4. Experimental

4.1. General

All solvents were dried by standard methods. Unless otherwise specified, chemicals were purchased from commercial suppliers, and used without further purification. TLC was performed on glass sheets pre-coated with silica gel (Kieselgel 60 F254, Merck). The ^{1}H and ^{13}C NMR spectrum were performed in $CDCl_3$ with TMS as an internal reference on a Bruker 400 NMR spectrometer, which operated at 400 MHz for ^{1}H and 100 MHz for ^{13}C nuclei. The chemical shifts were reported as δ values (ppm) relative to tetramethylsilane. High Resolution Mass Spectra (HRMS) were obtained on a JEOL JMS-AX 505WA mass spectrometer. The fluorescence measurements were performed on a Perkin–Elmer LS55 Luminescence Spectrometer.

4.2. Compound 2

A solution of dialdehyde **1** (94.4 mg, 0.1 mmol) and 2-aminobenzimidazole (46.6 mg, 0.35 mmol) in MeOH (5 mL)/CH_3CN (10 mL) was refluxed for 2 h. The progress of the reaction was monitored by TLC. Upon completion of the reaction, the solvent was evaporated, and the crude product was dissolved in a methanol and THF solvent mixture. The imine linkages of the product were reduced with an excess of $NaBH_4$ (38.8 mg, 1.0 mmol). The reaction mixture was stirred for 3 h. The solvent was evaporated, and water was poured into the content of the reaction mixture. After neutralization with 1 M HCl, the organic material was extracted with CH_2Cl_2 (3×50 mL). The organic layer was dried over anhydrous $MgSO_4$. After filtration and evaporation, the residue was purified by column chromatography on silica gel (hexane/EtOAc, 8:2) to give the compound **2** as a semisolid material (89 mg, 76%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.12 (s, 18H, CH_3), 1.24 (s, 18H, CH_3), 3.38 (d, 4H, $ArCH_2Ar$, J=12.8 Hz), 4.31–4.41 (m, 12H, CH_2, $ArCH_2Ar$), 4.67 (s, 4H, CH_2), 6.68 (d, 2H, Ar, J=8.0 Hz), 6.87–6.97 (m, 8H, Ar), 7.01 (s, 4H, Ar), 7.03 (s, 4H, Ar), 7.07 (d, 2H, Ar, J=7.2 Hz), 7.18 (t, 2H, Ar, J=8.0 Hz), 7.31 (d, 2H, Ar, J=7.2 Hz), 8.14 (br, 2H, NH), 8.73 (s, 2H, OH), 10.45 (br, 2H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.9 (CH_3), 31.0 (CH_3), 31.7 ($ArCH_2Ar$), 33.9 (Me_3C), 34.0 (Me_3C), 61.1 (CH_2), 67.3 (CH_2), 73.9 (CH_2), 112.3 (Ar), 120.5 (Ar), 121.0 (Ar), 121.3 (Ar), 125.0 (Ar), 125.3 (Ar), 125.8 (Ar), 127.9 (Ar), 128.1 (Ar), 128.2 (Ar), 132.5 (Ar), 135.9 (Ar), 142.2 (Ar), 147.6 (Ar), 149.7 (Ar), 150.0 (Ar), 157.0 (Ar), 160.7 (Ar); HRMS (FAB) calculated for $C_{76}H_{87}N_6O_6$ ($M+H^+$): 1179.6687, found 1179.6687.

4.3. Anion recognition studies

Anion binding ability of receptor **2** was performed using 10 μM of receptor **2** in CH_3CN. Measuring flasks were taken each containing 10 μM of receptor **2** along with varied amounts of a particular tetrabutylammonium dicarboxylate salt in CH_3CN. The solutions were kept at 25±1 °C for 3 h, and were shaken occasionally. Their fluorescence spectra were recorded with excitation at 335 nm.

Association constants K_a of **2** for pimelate and suberate were calculated by non-linear curve fitting using Eq. 1 in Kaleidagraph:[11]

$$I = I_0 + \frac{I_\infty - I_0}{2c_H}\left\{c_H + c_G + 1/K_a - \left[(c_H + c_G + 1/K_a)^2 - 4c_H c_G\right]^{1/2}\right\} \quad (1)$$

Association constants K_a of **2** for dicarboxylates showing 1:2 stoichiometry were calculated by using Eq. 2:[4d]

$$\log[(I - I_0)/(I_\infty - I)] = n \log c_G + \log K_a \quad (2)$$

where I_0 represents the fluorescence intensity of pure host, I represents the fluorescence intensity of receptor in the presence of guest, I_∞ is the fluorescence intensity in the presence of an excess of guest; c_H and c_G are the concentrations of host and guest, respectively.

In order to determine stoichiometry of the complex formed from receptor **2** and dicarboxylates, solutions of **2** and a particular tetrabutylammonium dicarboxylate salt were prepared as 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1. These solutions were kept at 25±1 °C for 3 h, and were shaken occasionally. Their fluorescence spectra were recorded at 465 nm. For interference evaluation, solutions were prepared containing receptor **2** (10 μM), one of the interfering dicarboxylate (malonate, succinate, glutarate, adipate or suberate), and (2, 4, 6, 8, 10, 15, and 20 μM) of tetrabutylammonium pimelate. The fluorescence intensity of each solution was recorded at 465 nm.

Acknowledgements

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Supplementary data

Fluorescence titrations of receptor **2** with various dicarboxylates and molecular modeling figure of receptor **2** are available. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.11.040.

References and notes

1. (a) Gale, P. A. *Acc. Chem. Res.* **2006**, *39*, 465–475; (b) Katayev, E. A.; Ustynyuk, Y. A.; Sessler, J. L. *Coord. Chem. Rev.* **2006**, *250*, 3004–3047; (c) Davis, A. P. *Coord. Chem. Rev.* **2006**, *250*, 2939–2951; (d) Schmidtchen, F. P. *Coord. Chem. Rev.* **2006**, *250*, 2918–2928; (e) Yoon, J.; Kim, S. K.; Singh, N. J.; Kim, K. S. *Chem. Soc. Rev.* **2006**, *35*, 355–360; (f) Bowman-James, K. *Acc. Chem. Res.* **2005**, *38*, 671–678; (g) Martínez-Máñez, R.; Sancenón, F. *Chem. Rev.* **2003**, *103*, 4419–4476; (h) Suksai, C.; Tuntulani, T. *Chem. Soc. Rev.* **2003**, *32*, 192–202; (i) Sessler, J. L.; Camiolo, S.; Gale, P. A. *Coord. Chem. Rev.* **2003**, *240*, 17–55; (j) Gale, P. A. *Coord. Chem. Rev.* **2003**, *240*, 167–189; (k) Gale, P. A. *Coord. Chem. Rev.* **2001**, *213*, 79–128; (l) Schmidtchen, F. P.; Berger, M. *Chem. Rev.* **1997**, *97*, 1609–1646.
2. (a) Liu, S.-Y.; He, Y.-B.; Wu, J.-L.; Wei, L.-H.; Qin, H.-J.; Meng, L.-Z.; Hu, L. *Org. Biomol. Chem.* **2004**, *2*, 1582–1586; (b) Voet, D.; Voet, J. G. *Biochemistry*, 2nd ed.; Wiley: New York, NY, 1995; (c) Nohta, H.; Sonoda, J.; Yoshida, H.; Satozono, H.; Ishida, J.; Yamaguchi, M. *J. Chromatogr., A* **2003**, *1010*, 37–44; (d) Miao, H.; Rubakhin, S. S.; Sweedler, J. V. *Anal. Chem.* **2005**, *77*, 7190–7194.
3. Carvalho, S.; Delgado, R.; Fonseca, N.; Felix, V. *New J. Chem.* **2006**, *30*, 247–257.
4. (a) Massimo, B.; Marco, B.; Alberto, M.; Dario, P.; Angelo, T. *New J. Chem.* **2007**, *31*, 352–356; (b) Gomy, C.; Schmitzer, A. R. *J. Org. Chem.* **2006**, *71*, 3121–3125; (c) Yen, Y.-P.; Ho, K.-W. *Tetrahedron Lett.* **2006**, *47*, 7357–7361; (d) Liu, S.-Y.; He, Y.-B.; Chan, W. H.; Lee, A. W. M. *Tetrahedron* **2006**, *62*, 11687–11696.
5. (a) Jang, Y. J.; Moon, B.-S.; Park, M. S.; Kang, B.-G.; Kwon, J. Y.; Hong, J. S. J.; Yoon, Y. J.; Lee, K. D.; Yoon, J. *Tetrahedron Lett.* **2006**, *47*, 2707–2710; (b) Kim, S. K.; Singh, N. J.; Kim, S. J.; Swamy, K. M. K.; Kim, S. H.; Lee, K.-H.; Kim, K. S.; Yoon, J. *Tetrahedron* **2005**, *61*, 4545–4550; (c) Boiocchi, M.; Bonizzoni, M.; Fabbrizzi, L.; Piovani, G.; Taglietti, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3847–3852; (d) Zeng, Z.-Y.; He, Y.-B.; Wu, J.-L.; Wei, L.-H.; Liu, X.; Meng, L.-Z.; Yang, X. *Eur. J. Org. Chem.* **2004**, 2888–2893; (e) Gunnlaugsson, T.; Davis, A. P.; O'Brien, J. E.; Glynn, M. *Org. Lett.* **2002**, *4*, 2449–2452; (f) Nishizawa, S.; Cui, Y.-Y.; Minagawa, M.; Morita, K.; Kato, Y.; Taniguchi, S.; Kato, R.; Teramae, N. *J. Chem. Soc., Perkin Trans. 2* **2002**, 866–870; (g) Mei, M.; Wu, S. *New J. Chem.* **2001**, *25*, 471–475.
6. (a) Singh, N.; Jang, D. O. *Org. Lett.* **2007**, *9*, 1991–1994; (b) Moon, K. S.; Singh, N.; Lee, G.; Jang, D. O. *Tetrahedron* **2007**, *63*, 9106–9111; (c) Kim, H. S.; Moon, K. S.; Jang, D. O. *Supramol. Chem.* **2006**, *18*, 97–101; (d) Kang, J.; Kim, H. S.; Jang, D. O. *Tetrahedron Lett.* **2005**, *46*, 6079–6082.
7. Seangprasertkji, R.; Asfari, Z.; Arnand, F.; Vicons, J. *J. Org. Chem.* **1994**, *59*, 1741–1744.
8. Iwamoto, K.; Araki, K.; Shinkai, S. *J. Org. Chem.* **1991**, *56*, 4955–4962.
9. (a) McFarland, S. A.; Finney, N. S. *J. Am. Chem. Soc.* **2002**, *124*, 1178–1179; (b) Fang, A. G.; Mello, J. V.; Finney, N. S. *Tetrahedron* **2004**, *60*, 11075–11087; (c) Kondo, S.; Kinjo, T.; Yano, Y. *Tetrahedron Lett.* **2005**, *46*, 3183–3186; (d) Kondo, S.-I.; Sato, M. *Tetrahedron* **2006**, *62*, 4844–4850; (e) Lee, D. H.; Im, J. H.; Lee, J.-H.; Hong, J.-I. *Tetrahedron Lett.* **2002**, *43*, 9637–9640; (f) Takeuchi, M.; Mizuno, T.; Shinmori, H.; Nakashima, M.; Shinkai, S. *Tetrahedron* **1996**, *52*, 1195–1204.
10. Job, P. *Ann. Chim.* **1928**, *9*, 113–203.
11. Valeur, B.; Pouget, J.; Bourson, J.; Kaschke, M.; Ernsting, N. P. *J. Phys. Chem.* **1992**, *96*, 6545–6549.
12. Amendola, V.; Boiocchi, M.; Fabbrizzi, L.; Palchetti, A. *Chem.—Eur. J.* **2005**, *11*, 120–127.
13. Shortreed, M.; Kopelman, R.; Kuhn, M.; Hoyland, B. *Anal. Chem.* **1996**, *68*, 1414–1418.