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Sensitive fluorescence sensor for nitroaniline isomers based on calix[4]arene bearing naphthyl groups

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ABSTRACT

Novel naphthyl-modified calix[4]arene was synthesized by click chemistry, and exhibited high affinity and selectivity for *p*-nitroaniline by the fluorescence spectroscopy. However, the sensitivity toward other anilines **3a**–**e** are negligible. The ^{1}H NMR, ^{1}H NOESY, MALDI-TOF mass spectroscopy and computational calculations revealed the formation of host–guest complex driven by H-bonding and hydrophobic interactions.

1. Introduction

The design of molecular recognition structures has attracted great interest in supramolecular chemistry.[1] In this connection, numerous investigations are now being carried out in both directed synthesis and studies of synthetic receptors and identification of the factors that determine interactions of the receptors with diverse analytes.[1b,2] The complexation properties of the host and guest have been extensively investigated by many means. Among them, the optical sensors (colorimetric or fluorescence) are much more popular and powerful tool to sense a variety of molecular and ionic guests.[3] It is noteworthy that design of host system is also essential for high affinity and selective recognition of analytes.

Macrocyclic compounds, specifically calixarenes have become a popular building block for the preparation of new host systems.[4] Application of calixarenes as molecular host is based, first of all, on their ability to bind selectively guest. Calixarenes have the ability to form supramolecular complexes by electrostatic, donor–acceptor, hydrophobic, and π–π stacking interactions of small molecules and ions with the aromatic system of the macrocyclic cavity. In ongoing efforts, even though some recognition of neutral organic compounds based on functionalized calixarenes have been reported,[5] the fluorescent method to sense molecular was relatively rare.[6] In this paper, we describe the design and click synthesis of fluorescent calix[4]arene **2**, which showed highly selective recognition toward *p*-nitroaniline **3f**. Compound **3f** is of importance because of its extremely common use as an intermediate in the synthesis of dyes, antioxidants, and pharmaceuticals.[7]

2. Results and discussion

The fluorescent calix[4]arene **2** was synthesized by click chemistry as shown in Scheme 1. Initially, the reaction of 2,3-naphthalenediol with 2.2 equiv of 2-azidoethyl 4-methylbenzenesulfonate in CH_3CN and K_2CO_3 as base gave the desired azide-functionalized naphthol **1** in high yield (Scheme S1). The reaction of alkynylcalixarene, was reacted with **1** using CuI as catalyst in toluene at 90 °C to give calix[4]arene **2**.[8] The structure of the compound was characterized by MALDI-TOF-MS spectra, elemental analyses, and ^{1}H and ^{13}C NMR studies (Fig. S4). The cone conformation is proven by two signals for the aromatic protons, two doublets for the bridging methylene groups, and two singlets for the *tert*-butyl groups in the ^{1}H NMR spectra.[9]

The molecular recognition behavior of the calix[4]arene **2** was studied toward aniline derivatives **3a**–**f** by fluorescence spectroscopy. Fig. 1 shows the fluorescence response of calix[4]arene **2** to 14 equiv of anilines (**3a**–**f**), including aniline, *o*-chloroaniline, *p*-chloroaniline, *o*-nitroaniline, *m*-nitroaniline, *p*-nitroaniline. Interestingly, *p*-nitroaniline can significantly quench the fluorescence of calix[4]arene **2**, but other of the aniline derivatives, such as *o*-nitroaniline, *m*-nitroaniline, had very little effect on fluorescence. It is well known that the nitro-aromatic compounds are a quenching

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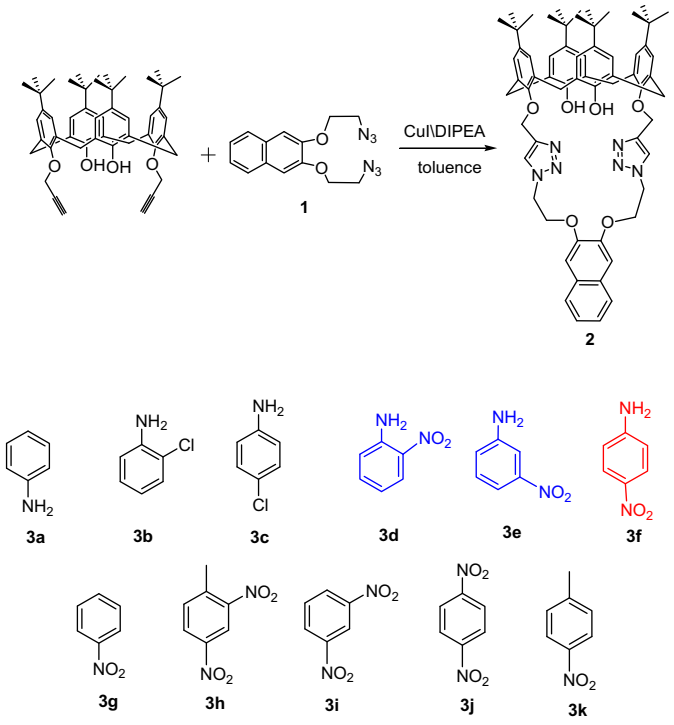

Scheme 1. Synthesis of calix[4]arene **2** and the structures of the guest.

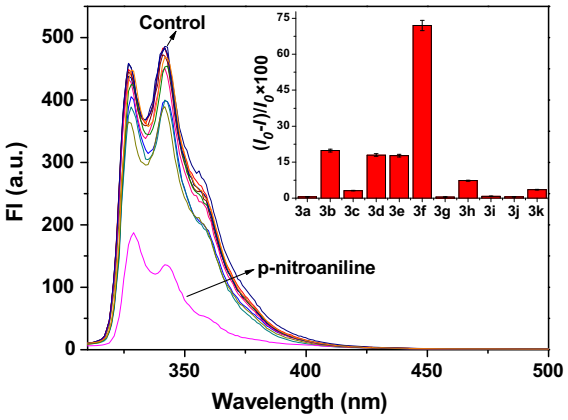

Fig. 1. Fluorescence intensity changes for calix[4]arene **2** (5×10^{-6} M) in CH_3CN upon addition of **3a**–**k** (5×10^{-5} M). Inset: $[((I_0-I)/I_0)]\times100$ (λ_{ex}=295 nm, Slit=5). I_0 is the fluorescent emission intensity of the host, and I is the fluorescent intensity after adding **3a**–**k**.

agent, which can induce the fluorescence quenching. In order to avoid the effect of the nitro-aromatic group, nitrobenzene, 2,4-dinitrotoluene, *m*-dinitrobenzene, 1,4-dinitrobenzene, and 4-methyl nitrobenzene (**3g**–**k**) as control guest were used to investigate the fluorescence response. It was found that the three nitro-aromatic compounds (**3g**–**i**) gave little fluorescence change, which showed that *p*-nitroaniline induced fluorescence quenching was not due to the interaction of the nitro-aromatic group.

The fluorescence spectra of **2** (5×10^{-6} M) at increasing concentrations of **3f** are depicted in Fig. 2a. It was found that while no shift in the fluorescence maximum was observed, the fluorescence intensities of **2** gradually decreased with the addition of increasing concentrations of **3f**. The association constant (K_a) of **2** for **3f** was calculated to be 2.06×10^4 M^{-1} by Benesi–Hilderbrand equation.[10] In the Job plot a maximum fluorescence change was observed when the molar fraction of **2** versus **3f** was 0.5, indicative of a 1:1

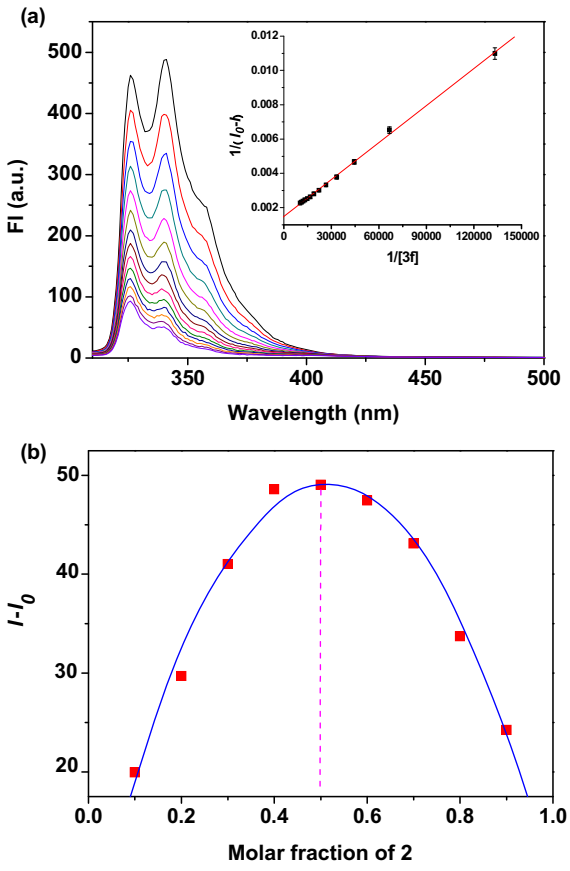

Fig. 2. (a) Fluorescence spectra titration of **2** (5×10^{-6} M) with various equivalents of **3f** in CH_3CN (0, 1.5, 3, 4.5, 6, 7.5, 9, 10.5, 12, 13.5, 15, 16.5, 18, 19.5, 22.5 equiv, λ_{ex}=295 nm, Slit=5). Inset: Benesi–Hildebrand analysis of the fluorescence changes for the complexation between **2** and **3f** (λ_{ex}=295 nm, Slit=5). (b) Job's plots of **2** toward **3f** in CH_3CN solution at an invariant total concentration of 5×10^{-6} M (λ_{ex}=295 nm, Slit=5).

complex (Fig. 2b).[11] The 1:1 complex of **2** and **3f** has been further revealed based on MALDI mass spectrum (Fig. S1), which exhibited the peak at *m*/*z* 1163.0 (calcd=1162.4) corresponding to $[\mathbf{2}+\mathbf{3f}+H]^+$.

An important feature of **2** is high binding affinity toward **3f** over other aniline. Based on fluorescence titration experiments between **2** and other anilines derivatives, including *o*-chloroaniline, *p*-chloroaniline, *o*-nitroaniline, *m*-nitroaniline (Fig. S2), the association constants (K_a) were determined as shown in Table 1. Compared to the K_a, the $K_{a_{2-3f}}$ is highest, which indicated the stronger bind of **2** for **3f**.

The selectivity of **2** (5.0×10^{-6} M) to *p*-NAE (5.0×10^{-5} M) was further demonstrated in the presence of 10 equiv of other competitive species. As shown in Fig. 3, the presence of **3a**–**e** and **3g**–**i** does not significantly interfere the **3f** selectivity, which suggested that **2** can be used as a potential chemosensor for **3f**.

To seek further more detailed information on the binding properties of **2** with **3f**, the ^1H NMR spectra of **2**, **3f**, mixed **2** with **3f** was investigated as depicted in Fig. 4. The signals of protons on the aromatic ring of **3f** underwent upfield shifting (Ha, 0.063 ppm; Hb, 0.214 ppm). Meanwhile, the proton of NH_2 in **3f** (Hc) and the proton of ArOH of calix[4]arene **2** disappeared. This phenomenon may attribute to H-bonding interactions between NH_2 group of **3f** and the phenolic OH of **2**.[12] Because of the reciprocity, the protons on the bridging methylene groups of calix[4]arene **2** was upfield shifted (Hd, 0.017 ppm; He, −0.002 ppm). The upfield shifts of aromatic ring of **3f** and the remarkable shift of Hb (**3f**) indicated that the **3f** penetrated into the rich-electron cavity of the host calix[4]arene from the NH_2 end of the benzene ring. Overall, the binding of

Table 1
The complex constants between **2** and other anilines derivatives

	3b	3c	3d	3e	3f
K_a (10^3)	6.311	6.858	0.445	0.868	20.54

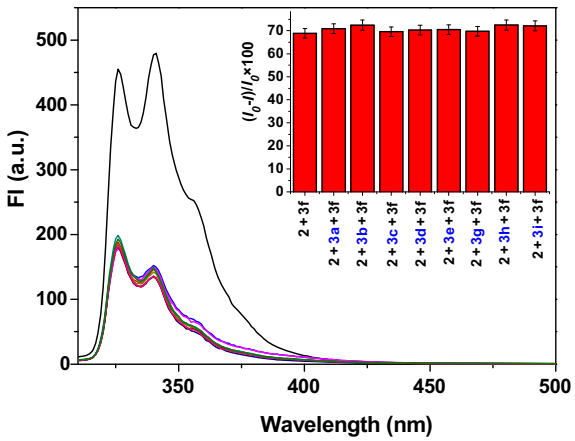

Fig. 3. The fluorescence changes of **2** (5×10^{-6} M) toward 10 equiv **3f** in the presence of 10 equiv competitive species. I_0 is fluorescence emission intensity at 341 nm for free **2**, and I is the fluorescent intensity upon addition of competitive species with the existence of **3f** (λ_{ex}=295 nm, Slit=5).

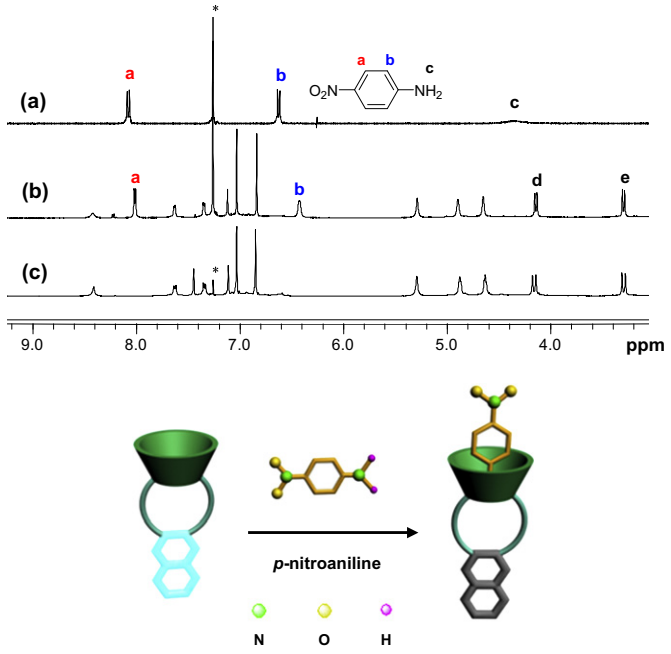

Fig. 4. The partial ^{1}H NMR spectra ($CDCl_3$, 400 MHz, 298 K) of (a) **3f** (8 mM) (b) **2** and **3f** (8 mM each) (c) **2** (8 mM); and schematic representation of the possible recognition process for **2** toward **3f** via host–guest interaction.

3f penetrated into the hydrophobic cavity of calix[4]arene **2** is driven by H-bonding between NH_2 group of guest and the phenolic OH of host, hydrophobic interactions, and a cavity effect. While NOESY experiments could be extremely valuable to verify the inclusion nature of these complexes, since one can conclude that two protons are closely located in space. To get further information about the geometry of the inclusion complexation between the calixarene and *p*-nitroaniline, the NOESY spectrum was performed. As shown in Fig. S3, the NOESY spectrum of an equimolar mixture of host **2** with *p*-nitroaniline (8.0 mM each) displays clear NOE cross-peaks between the Hb protons close to the NH_2 end of *p*-nitroaniline and the aromatic protons of calix[4]arene **2**.[13] The result indicated the *p*-nitroaniline was included in the hydrophobic cavity of calix[4]arene **2** from the NH_2 end. The inclusion complex form between **2** and **3f** through the host and guest inclusion induces a strong fluorescence quenching due to a well-defined electron transfer process from the fluorophore to the guest.[14] A plausible complexation mode is therefore depicted in Fig. 4.

The binding of calix[4]arene **2** and **3f** was also examined by computational calculations at b3lyp/6-31G(d) levels using Gaussian 03.[15] The results from molecular mechanics calculation were generally consistent with the ^{1}H NMR and fluorometric experimental results. Fig. 5 shows the top view of the optimized structure of the host–guest complex. Compound **3f** was partially located inside hydrophobic cavity of the cone calix[4]arene from the NH_2 end of the benzene ring. by two NH···OAr H-bonds (d_1=3.3 Å, d_2=3.4 Å) between calixarene hydroxyls and NH_2 of **3f**.

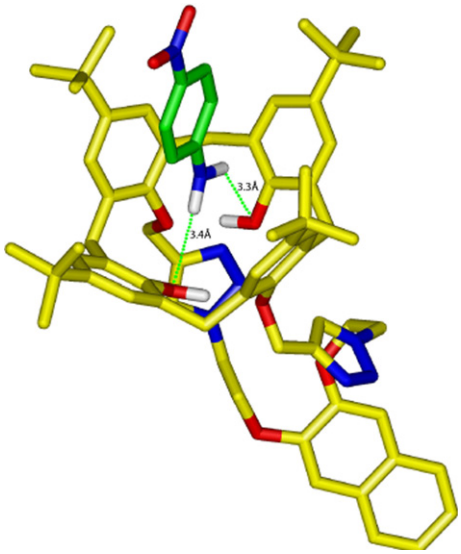

Fig. 5. The top view on the optimized structure of the inclusion complex of **2** with **3f**.

3. Conclusions

In conclusion, we have synthesized a fluorescent calix[4]arene by click chemistry, which exhibits high binding affinity and selectivity toward *p*-nitroaniline (**3f**). Job's plots and MALDI-TOF mass spectrum showed a 1:1 stoichiometry complexation between of **2** toward **3f**. By a combination of H-bonding and hydrophobic interactions as revealed by ^{1}H NMR, ^{1}H NOESY, and computational calculations, **2** and **3f** complex was formed. The electron-poor aromatic guests were included in the electron-rich cavity of the host calix[4]arene within a 1:1 complex mode, which induce the fluorescence quenching. The reasonable sensor design is an effective strategy to reinforce the binding affinity and fluorescence modulation.

4. Experimental section

4.1. Instruments

^{1}H NMR and ^{13}C NMR spectra were recorded on Varian Mercury VX400 instrument at ambient temperature with TMS as the internal standard. ^{1}H NOESY spectra was recorded on Varian Mercury VX600 instrument at ambient temperature with TMS as the internal standard. Chemical shifts are expressed in parts per million and *J* values are given in hertz. MALDI-TOF-MS were recorded on matrix assisted laser desorption ionization/time of flight MS. PL spectra were

recorded on a Cary Eclipse instrument. Computational calculations were recorded at b3lyp/6-31G(d) levels using Gaussian 03. All chemicals were A.R. grade and were purified by standard procedures.

4.2. The procedure for the synthesis of calix[4]arene 2

A mixture of alkynylcalixarene (0.15 g, 0.20 mmol), azide-functionalized naphthol derivatives **1** (0.06 g, 0.20 mmol), DIPEA (213 μL, 1.20 mmol), and the copper catalyst CuI (0.04 g, 0.11 mmol) in toluene (80 mL) was reacted under reflux for 12 h. Evaporation of the solvent yields a crude that was purified by column chromatography (AcOEt–PE 2:1) giving **2** (0.10 g, 50%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.98 (s, 18H, $C(CH_3)_3$), 1.26 (s, 18H, $C(CH_3)_3$), 3.28 (d, J=13.1 Hz, 4H, $ArCH_2Ar$), 4.14 (d, J=13.1 Hz, 4H, $ArCH_2Ar$), 4.61 (t, J=4.1 Hz, 4H, NCH_2), 4.86 (s, 4H, OCH_2), 5.28 (s, 4H, $ArOCH_2$), 6.33 (s, 4H, ArH), 7.01 (s, 4H, ArH), 7.09 (s, 2H, ArOH), 7.32 (q, J=3.1 Hz, 2H, Naphth), 7.43 (s, 2H, Naphth), 7.61 (q, J=4.7 Hz, 2H, Naphth), 8.39 (s, 2H, NCH) ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.0, 31.6 (CH_3), 31.9 ($ArCH_2Ar$), 33.78, 33.9 ($C(CH_3)_3$), 50.3 (CH_2N), 67.4 (OCH_2), 70.3 ($ArOCH_2$), 109.7, 124.8, 125.1, 125.7, 126.4, 127.7, 129.4, 132.5, 141.9, 147.4, 148.0, 150.2, 150.3 (ArC, NCH, NC, NaphthC); MALDI-TOF-MS calcd for $C_{64}H_{74}N_6O_6Na$: $[M+Na]^+$ 1045.6, found: 1045.7 $[M+Na]^+$; Anal. Calcd for $C_{64}H_{74}N_6O_6$: C, 75.12; H, 7.29; N, 8.21; found: C, 75.16; H, 7.25; N, 8.27%.

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Supplementary data

Experimental details, MALDI-TOF mass spectrum of **2**·*p*-NAE complex; fluorescence spectra titration of **2** with **3b**–**e**; ^{1}H NOESY spectrum of a mixture of **2** with the *p*-nitroaniline **3f**; NMR and MS spectra for compound **2**. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.04.076.

References and notes

1. (a) Lehn, J. M.; Meric, R.; Vigneron, J. P.; Guilhem, J.; Pascard, C.; Asfari, Z.; Vicens, J. *Supramol. Chem.* **1995**, *5*, 97; (b) Danil de Namor, A. F.; Cleverley, R. M.; Zapata-Ormachea, M. L. *Chem. Rev.* **1998**, *98*, 2495; (c) Armaid-Net, F.; Fuangswasdi, S.; Notti, A.; Pappalardo, S.; Parisi, M. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 112; (d) Kuwabara, T.; Nakajima, H.; Nanasawa, M.; Ueno, A. *Anal. Chem.* **1999**, *71*, 2844; (e) Beer, P. D.; Gale, P. A.; Chen, G. Z. *Coord. Chem. Rev.* **1999**, *186*, 3.
2. (a) Beer, P. D.; Gale, P. A.; Chen, G. Z. *J. Chem. Soc., Dalton Trans.* **1999**, *12*, 1897; (b) Ikeda, A.; Shinkai, S. *Chem. Rev.* **1997**, *97*, 1713; (c) Yordanov, A. T.; Roundhill, D. M. *Coord. Chem. Rev.* **1998**, *170*, 93.
3. (a) de Silva, A. P.; Vance, T. P.; West, M. E. S.; Wright, G. D. *Org. Biomol. Chem.* **2008**, *6*, 2468; (b) Wright, A. T.; Anslyn, E. V. *Chem. Soc. Rev.* **2006**, *35*, 14.
4. Gutsche, C. D. *Calixarenes Revisited; Monographs in Supramolecular Chemistry*; The Royal Society of Chemistry: Cambridge, 1989; Vol. 1.
5. (a) Paci, B.; Deleuze, M. S.; Caciuffo, R.; Tomkinson, J.; Ugozzoli, F.; Zerbetto, F. *J. Phys. Chem. A* **1998**, *102*, 6910; (b) Kunsági-Máté, S.; Szabó, K.; Lemli, B.; Bitter, I.; Nagy, G.; Kollár, L. *Thermochim. Acta* **2005**, *425*, 121; (c) Kunsági-Máté, S.; Nagy, G.; Jurecka, P.; Kollár, L. *Tetrahedron* **2002**, *58*, 5119; (d) Kunsági-Máté, S.; Bitter, I.; Grun, A.; Nagy, G.; Kollár, L. *J. Biochem. Biophys. Methods* **2002**, *53*, 101; (e) Li, W. Y.; Li, H.; Zhang, G. M.; Chao, J. B.; Ling, L. X.; Shuang, S. M.; Dong, C. *J. Photochem. Photobiol., A* **2008**, *197*, 389.
6. Lee, Y. H.; Liu, H.; Lee, J. Y.; Kim, S. H.; Kim, S. K.; Sessler, J. L.; Kim, Y.; Kim, J. S. *Chem.—Eur. J.* **2010**, *16*, 5895.
7. Costela, A.; Garcia-Moreno, I.; Dabrio, J.; Sastre, R. *J. Photochem. Photobiol., A* **1997**, *109*, 77.
8. Morales-Sanfrutos, J.; Ortega-Munoz, M.; Lopez-Jaramillo, J.; Hernandez-Mateo, F.; Santoyo-Gonzalez, F. *J. Org. Chem.* **2008**, *73*, 7768.
9. (a) Choi, J. K.; Lee, A.; Kim, S.; Ham, S.; No, K.; Kim, J. S. *Org. Lett.* **2006**, *8*, 1601; (b) Xu, Z. C.; Qian, X. H.; Cui, J. N. *Org. Lett.* **2005**, *7*, 3029.
10. (a) Benesi, H. A.; Hildebrand, J. H. *J. Am. Chem. Soc.* **1949**, *71*, 2703; (b) Kim, J. S.; Quang, D. T. *Chem. Rev.* **2007**, *107*, 3780.
11. Job, P. *Ann. Chim.* **1928**, *9*, 113.
12. Chang, K. C.; Su, I. H.; Wang, Y. Y.; Chung, W. S. *Eur. J. Org. Chem.* **2010**, 4700.
13. Shivanyuk, A. *J. Am. Chem. Soc.* **2007**, *129*, 14196.
14. Metivier, R.; Leray, I.; Valeur, B. *Chem.—Eur. J.* **2004**, *10*, 4480.
15. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Gonzalez, C.; Pople, J. A. *Gaussian 03, Revision C.02*; Gaussian: Wallingford CT, 2004.