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Ion-Induced FRET On−Off in Fluorescent Calix[4]arene

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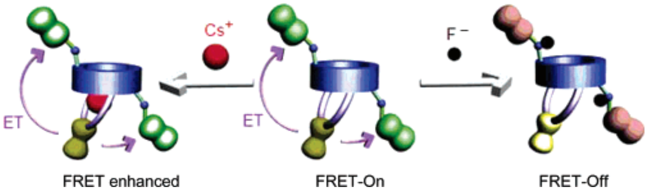

A novel calix[4]arene bearing one 2,3-naphthocrown-6 and two coumarin amide units at the lower rim in *partial-cone* conformation (**1**) was synthesized as a colorimetric and FRET-based fluorometric sensor for F^- and Cs^+ ions. Intramolecular FRET from the naphthalene emission to the coumarin absorption affords high fluorescence selectivity toward F^- and Cs^+ ions.

Fluorometry is becoming important for ion sensing because of its simplicity, high selectivity, and sensitivity.[1] Design of a fluorescence sensor requires a molecule that possesses two functional units: an ionophore responsible for selectively binding ions and a fluorophore responsible for signal transduction. Most fluorometric sensors are designed to adopt photophysical changes produced upon complexation including photoinduced electron transfer (PET),[2] photoinduced charge transfer (PCT),[3] excimer/exciplex formation and extinction,[4,5] or fluorescence resonance energy transfer (FRET).[6] There are numerous reports concerning ion sensors based on PCT, PET, and excimer/exciplex. The FRET is known to be sensitive, selective, and adaptable to a wide variety of systems;[7,8] however, the reports on FRET-based ion sensors are still at a modest number.

FRET arises from an interaction between a pair of fluorophores in their excited states. By a long-range dipole−dipole coupling mechanism, the excited state of a fluorescent donor is then nonradiatively transferred to the acceptor and the donor returns to its electronic ground state. Therefore, the FRET is required to have a certain extent of spectral overlap between the emission spectrum of the donor and the absorption spectrum of the acceptor.[9,10]

In a previous paper,[11] we reported a calix[4]arene with two coumarin groups at the lower rim acting as a fluoride-selective sensor. The addition of fluoride ion into this compound causes a strong quenching of fluorescence intensity with a red shift of the emission band, which can be explained by photoinduced charge transfer (PCT).

Keeping previous researches above in mind, we thought the attachment of both naphthalene and coumarin groups to a calix[4]arene could provide a compound such that there is a FRET from an excited donor (naphthalene) to a nearby acceptor (coumarin), and the FRET efficiency is variable with the anion added. Besides, the naphthalene group is designed to link to calix[4]arene through a crown-6 loop, which is capable of binding the Cs^+ ion effectively, which can promote the variation of the FRET efficiency.[12] These two ions have received interest from chemists for their biological and environmental effects. F^- ion is known to be essential to human beings at low concentrations, but potentially toxic at higher levels,[13,14] while the radio-active Cs^+ ion can damage living organisms.[15]

In this paper, we report the synthesis and the fluorometric properties of a calix[4]arene **1** as well as its sensing ability for both cations and anions with respect to the FRET changes. The colorimetric ion sensing ability is also studied and presented herein.

As shown in Scheme 1, reaction of calix[4]arene with 2,3-naphthoglycolic ditosylate (**2**)[16] under basic medium gave **3** in 30% yield. Although only 1.0 equiv of ditosylate was used, the reaction yield is quite low due to the preferential formation of calix[4]biscrown-6.[16] Synthesis of **1** was performed by the condensation of acylated 7-amino-4-(trifluoromethyl)coumarin

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[1] (a) Kim, S. K.; Lee, S. H.; Lee, J. Y.; Lee, J. Y.; Bartsch, R. A.; Kim, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 16499. (b) Kim, S. K.; Bok, J. H.; Bartsch, R. A.; Lee, J. Y.; Kim, J. S. *Org. Lett.* **2005**, *7*, 4839. (c) Cho, E. J.; Moon, J. W.; Ko, S. W.; Lee, J. Y.; Kim, S. K.; Yoon, J.; Nam, K. C. *J. Am. Chem. Soc.* **2003**, *125*, 12376.

[2] (a) Aoki, L.; Sakaki, T.; Shinkai, S. *J. Chem. Soc., Chem. Commun.* **1992**, 730. (b) Jin, T.; Ichikawa, K.; Koyama, T. *J. Chem. Soc., Chem. Commun.* **1992**, 499. (c) Ji, H.-F.; Brown, G. M.; Dabestani, R. *Chem. Commun.* **1999**, 609. (d) Kim, J. S.; Shon, O. J.; Rim, J. A.; Kim, S. K.; Yoon, J. *J. Org. Chem.* **2002**, *67*, 2348. (e) Kim, J. S.; Noh, K. H.; Lee, S. H.; Kim, S. K.; Kim, S. K.; Yoon, J. *J. Org. Chem.* **2003**, *68*, 597.

[3] Leray, I.; Lefevre, J. P.; Delouis, J. F.; Delaire, J.; Valeur, B. *Chem. Eur. J.* **2001**, *7*, 4590.

[4] Birks, J. B. *Photophysics of Aromatic Molecules*; Wiley-Interscience: London, UK, 1970.

[5] Lee, S. H.; Kim, S. H.; Kim, S. K.; Jung, J. H.; Kim, J. S. *J. Org. Chem.* **2005**, *70*, 9288.

[6] Hecht, S.; Vladimirov, N.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **2001**, *123*, 18.

[7] Tsien, R. Y.; Miyawaki, A. *Science* **1998**, *280*, 1954.

[8] Weiss, S. *Science* **1999**, *283*, 1676.

[9] Lakowicz, J. R., Ed. *Principles of Fluorescence Spectroscopy*; Plenum Publishers Corporation: New York, 1999.

[10] Stryer, L.; Haugland, R. P. *Proc. Natl. Acad. Sci. U.S.A.* **1967**, *58*, 719.

[11] Lee, S. H.; Kim, H. J.; Lee, Y. O.; Vicens, J.; Kim, J. S. *Tetrahedron Lett.* **2006**, *47*, 4373.

[12] Casnati, A.; Ungaro, R.; Asfari, Z.; Vicens, J. In *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Eds.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 2001; p 365.

[13] Camargo, J. A. *Chemosphere* **2003**, *50*, 251.

[14] Cerklewski, F. L. *Nutr. Res.* (*N.Y., NY, USA*) **1997**, *17*, 907.

[15] Gaur, S. *J. Chromatogr. A* **1996**, *733*, 57.

[16] (a) Asfari, Z.; Bressot, C.; Vicens, J.; Hill, C.; Dozol, J.-F.; Rouquette, H.; Eymard, S.; Lamare, V.; Tournois, B. *Anal. Chem.* **1995**, *67*, 3133. (b) Zouhair, A.; Pierre, T.; Martine, N.; Vicens, J. *Tetrahedron Lett.* **1999**, *40*, 499.

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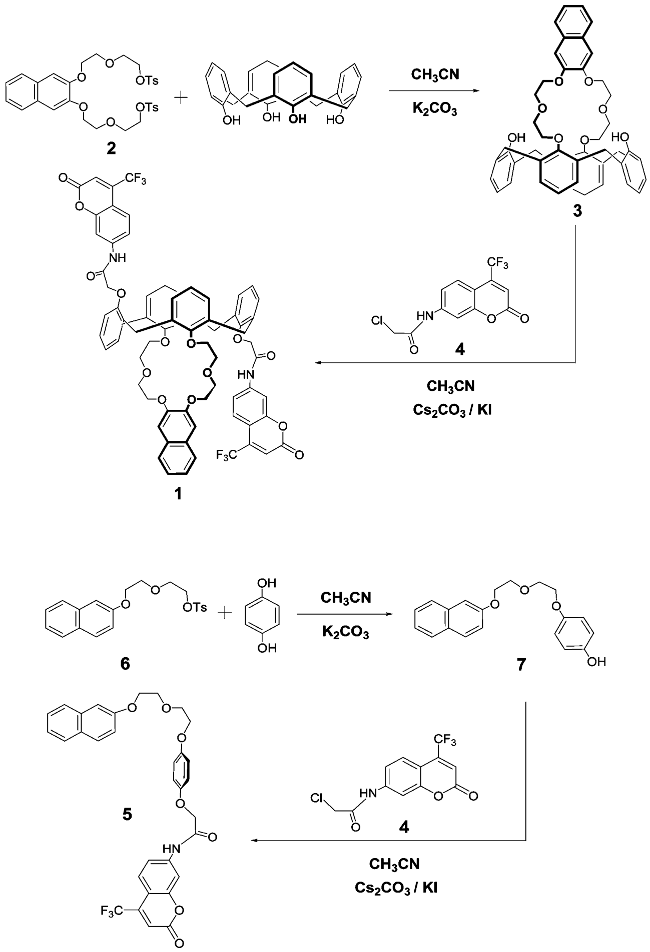
SCHEME 1. Synthetic Pathways to 1 and 5



(**4**)[11] with *cone*-calix[4]monocrown-6 (**3**) in the presence of Cs_2CO_3 as a base and a catalytic amount of KI. Unexpectedly, we obtained **1** in the *partial-cone* conformation instead of the *1,3-alternate* one, which may show a stronger binding ability toward alkali metal cation.[12] ^{1}H NMR peaks of **1** at 4.48, 3.75, and 3.22 ppm for 8 hydrogen atoms of $ArCH_2Ar$ and ^{13}C NMR peaks of $ArCH_2Ar$ at 38.0 and 32.0 ppm clearly indicate that it is in the fixed *partial-cone* conformation.[17,18] To prove the fact of the CHEF effect and FRET in compound **1**, reference material **5** was also prepared as shown in Scheme 1.

1 contains two amide groups capable of binding anions[11] and one crown-6 loop as a binding site for metal cations.[12] Free **1** displays two strong absorption bands at 242 and 344 nm arising from the naphthalene and the coumarin moieties, respectively, which are confirmed by the absorption spectra of the reference materials **3** and **4** (Figure S1, Supporting Information). Also, **1** shows weak naphthalene emission bands ranging from 326 to 340 nm along with a broad coumarin emission band at 422 nm with an excitation at 245 nm (Figure S2, Supporting Information). Then the spectral overlap between naphthalene emission and coumarin absorption is optimized to provide the FRET On. As seen in Figure S1 (Supporting Information), F^- binding promotes a red-shift of the coumarin absorption band by 91 nm, which is due to an anion binding driven photoinduced charge transfer (PCT).[11] As a result, the spectral overlap between the donor and the acceptor does not give the FRET Off.

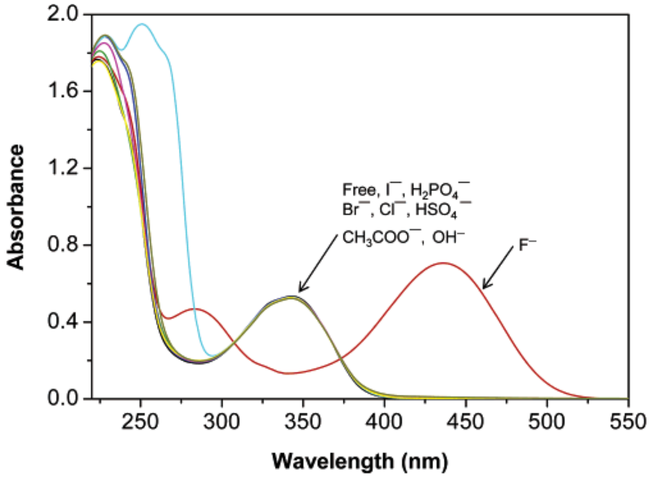


FIGURE 1. Absorption spectra of **1** (20.0 μM) upon addition of TBA^+ salts of F^-, Cl^-, Br^-, I^-, CH_3COO^-, OH^-, HSO_4^-, and $H_2PO_4^-$ (10.0 mM) in CH_3CN.

SCHEME 2. Complexation Mechanism of 1 with F−

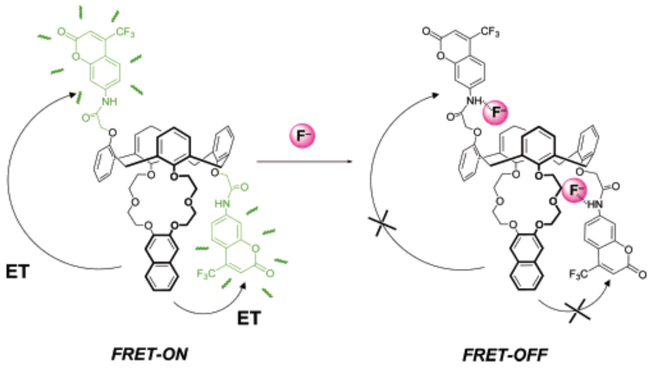


Figure 1 shows absorption changes of **1** upon addition of F^-, Cl^-, Br^-, I^-, CH_3COO^-, OH^-, HSO_4^-, and $H_2PO_4^-$. Only the F^- ion induces a significant red-shift of the coumarin absorption from 344 to 435 nm. Additionally, fluorescence changes of **1** upon the addition of various anions exhibit an especially high selectivity toward fluoride ion (Figure S2, Supporting Information). Therefore, we envisioned that these fluorescence and absorption changes associated with the mechanism in Scheme 2 could potentially be applicable to the development of a selective chemosensor for fluoride ion in CH_3CN. In the fluoride titration absorption spectra, we can observe two clear isosbestic points at 306 and 372 nm (Figure S3, Supporting Information). The red-shift from 344 to 435 nm of the coumarin band is attributed to H-bonding between amide N−H and F^- followed by deprotonation along with a visual color change from colorless to pale yellow. The color change was not observed until addition of fluoride ion up to 20 equiv (Figure S4, Supporting Information). The color only remained unchanged for a short period (less than 5 min) and turned deep yellow after that. Therefore, all experiments were immediately carried out after the preparation of samples.

Figure 2 indicates fluorescence changes upon fluoride anion titration. Upon addition of F^- in **1**, red-shifted coumarin emissions appear at 536 nm due to the PCT mechanism[11] and

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(17) Neri, P.; Bottino, A.; Geraci, C.; Piattelli, M. *Tetrahedron*: *Asymmetry* **1996**, *7*, 17.

(18) Louati, A.; Spraula, J.; Gabelica, V.; Kuhn, P.; Matt, D. *Electrochem. Commun.* **2006**, *8*, 761.

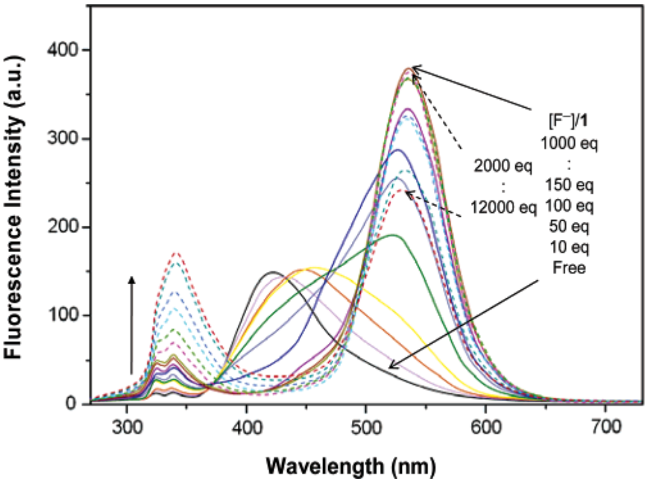

FIGURE 2. Fluorescence spectra of **1** (6.0 μM) upon addition of various concentrations of $TBA^+ F^-$ in CH_3CN with an excitation at 245 nm.

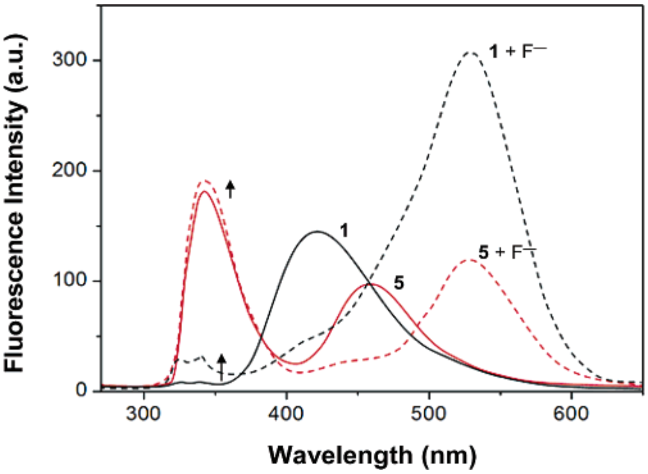

FIGURE 3. Fluorescence spectra of **1** (6.0 μM) and **5** (6.0 μM) upon addition of $TBA^+ F^-$ in CH_3CN with an excitation at 245 nm: (solid line) ligand only; (dashed line) ligand + F^- (0.6 mM).

the naphthalene emission at 342 nm concomitantly increases, which can be referred to as FRET-off induced by a minimized spectral overlap between the donor emission and the acceptor absorption band (Scheme 2 and Figure S1). Addition of 1000 equiv of F^- gives a quenched coumarin emission, which is presumably due to the photoinduced electron transfer (PET) from F^- to the coumarin unit.

To gain insight into a role of the calix[4]arene framework in **1** on this FRET effect, the photophysical property of **1**·F^- was compared with that of reference **5**·F^-. As shown in Figure 3, **5** displays a stronger naphthalene emission at 342 nm than does **1**, implying that the FRET efficiency from naphthalene to coumarin in **1** is larger than that in **5**. This is presumably because unlike **5**, **1** with a calix[4]arene framework in the organic solvent has a greater conformational rigidity with respect to the favorable distance capable for the FRET between the naphthalene and the coumarin. Then, addition of F^- to a solution of **1** increases the naphthalene emission because the FRET declined whereas addition of F^- rarely changes the naphthalene emission of **5**. From the titration experiment, association constants of **1** and **5** for F^- in CH_3CN were calculated to be 5.7×10^4 and 1.9×10^3 M^{-1} (Figures S3, S,7 and S8, Supporting Information), respectively.[19] For the FRET efficiency, we can also estimate through the following equation[20]

$$E = 1 - (F'_{D}/F_{D})$$

where E denotes the FRET efficiency and F'_D and F_D are the donor fluorescence intensity with and without an acceptor, respectively. E of **1**, **5**, **1**·F^-, and **5**·F^- was calculated to be 0.95, 0.66, 0.79, and 0.62, respectively. So, it is noteworthy that the FRET change of **1** with calixarene platform is more considerable than that of **5** in the presence of F^-, which means **1** responds to the F^- ion more sensitively than **5**.

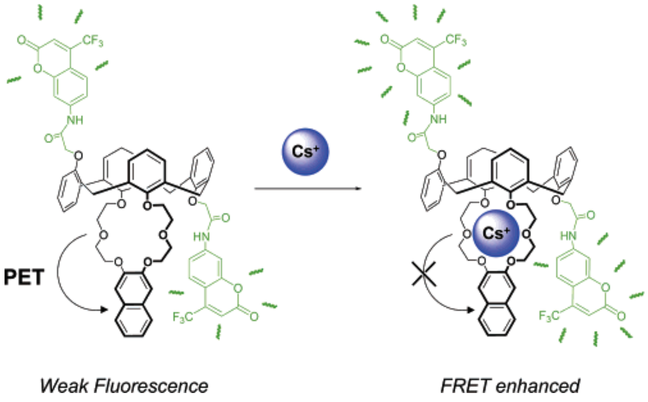

FIGURE 4. Complexation mechanism of **1** with Cs^+.

For the binding interaction between **1** and fluoride ion, NMR tirations of the $CDCl_3$ solution of **1** with fluoride ion were carried out (Figure S9, Supporting Information). The intensity of the amide proton signal decreases continuously with addition of fluoride ion and vanishes at 0.58 equiv, which can be explained by N−H deprotonation promoted by (i) the intrinsic acidity of **1** enhanced by conjugation of nitrogen lone-pair electrons with the aromatic ring and (ii) the high stability of the $[HF_2]^-$ hydrogen-bonding complex.

In addition to evaluating a response of **1** for anions, those for cations with perchlorate salts were also carried out. There is no significant absorption change of **1** in intensity as well as in wavelength upon addition of cations (Figure S10, Supporting Information). The fluorescence intensity changes ($I - I_0$) of both **1** and **5** upon addition of various cations are listed in Figure S11 (Supporting Information). The results indicate that **1** exhibits a high selectivity for the Cs^+ ion. It is known that the Cs^+ ion is favorably encapsulated in the calixcrown-6-ether ring and the K^+ ion prefers to be encapsulated in the crown-5-ether ring because of the size complementarities along with the π-metal complexation concept.[12] Association constants of **1** for Cs^+ and K^+ ions estimated from spectrophotometric titrations are 5.4×10^2 and 1.6×10^2 M^{-1}, respectively.[19]

Interestingly, we observed that the coumarin emission of **1** is markedly enhanced when the Cs^+ ion is added to a solution of **1**. This is because the CHEF (chelating enhanced fluores-

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(19) (a) Association constants were calculated with the computer program ENZFITTER, available from Elsevier-BIOSOFT: 68 Hills Road, Cambridge CB2 1LA, United Kingdom. (b) Connors, K. A. *Binding Constants*; Wiley: New York, 1987.

(20) Lakowicz, J. R. *Principles of Fluorescence Spectroscopy*, 2nd ed.; Kluwer Academic/Plenum: New York, 1999; Chapter 13.

cence) upon complexation with the Cs^+ ion leads to the repression of the PET from oxygen atoms to the naphthalene group, making the spectral overlap (FRET) between donor emission (naphthalene) and acceptor absorption (coumarin) more effective. In contrast, reference **5**, which has neither crown-6 nor calix[4]arene, does not show any fluorescence changes under the same condition, confirming that the calixcrown-6 part plays a key role in the Cs^+ ion binding to enhance the FRET efficiency.

In conclusion, FRET-based colorimetric and fluorometric calix[4]arene was developed. The FRET efficiency driven from naphthalene to coumarin in **1** with the calix[4]arene platform is larger than that in **5**. The F^- selectivity over that of other anions was observed from the extent of the FRET change of **1**. Besides, regarding the FRET changes, we observed that **1** shows the Cs^+ ion selectivity over that of other metal cations. Addition of the Cs^+ ion to **1** provides an enhanced FRET in **1** because of repression of the PET from oxygen atoms to the naphthalene group, making the spectral overlap (FRET) between the donor emission (naphthalene) and the acceptor absorption (coumarin) more effective.

Experimental Section

Preparation of 1. Under nitrogen, a solution of **3** (1.00 g, 1.38 mmol), **4** (1.26 g, 4.14 mmol), Cs_2CO_3 (0.67 g, 2.07 mmol), and a catalytic amount of KI in CH_3CN (20 mL) was heated at 80 °C. After refluxing for 24 h, the mixture was dissolved in CH_2Cl_2 (100 mL) and treated with dilute HCl. The organic layer was washed with water (300 mL), dried over anhydrous $MgSO_4$, and filtered. Purification by chromatography on silica gel (ethyl acetate/hexane, 1:2) allowed the isolation of **1** as a yellowish solid in 20% (0.34 g) yield. Mp 178−180 °C. IR (KBr pellet, cm^{-1}): 1650, 1725, 1515. FAB MS *m*/*z* (M^+) calcd 1262.3, found 1263.0. Anal. Calcd for $C_{70}H_{56}F_6N_2O_{14}$: C, 66.56; H, 4.47; N, 2.22. Found: C, 66.56; H, 4.65; N, 2.12.

Preparation of 5. Under nitrogen, a solution of **7** (0.30 g, 0.92 mmol), **4** (0.43 g, 1.43 mmol), and Cs_2CO_3 (0.13 g, 0.92 mmol) in CH_3CN (30 mL) was heated at 80 °C. After refluxing for 24 h, the mixture was dissolved in CH_2Cl_2 (100 mL) and treated with dilute HCl. The organic layer was washed with water (300 mL), dried over anhydrous $MgSO_4$, and filtered. Recrystallization from MeOH produced 0.30 g (60%) of **5** as a yellow solid. Mp 130−140 °C. IR (KBr pellet, cm^{-1}): 1720, 1121. FAB MS *m*/*z* (M^+) calcd 593.5, found 594.0. Anal. Calcd for $C_{32}H_{26}F_3NO_7$: C, 65.75; H, 4.42. Found: C, 65.76; H, 4.40.

Preparation of 7. Under nitrogen, a solution of hydroquinone (0.30 g, 2.70 mmol), **6** (1.05 g, 2.70 mmol), and K_2CO_3 (0.19 g, 1.40 mmol) in CH_3CN (30 mL) was heated at 80 °C. After refluxing for 24 h, the mixture was dissolved in CH_2Cl_2 (100 mL) and treated with dilute hydrochloric acid. The organic layer was washed with water (300 mL), dried over anhydrous $MgSO_4$, and filtered. Purification by chromatography on silica gel (ethyl acetate/hexane, 1:4) allowed the isolation of **7** as a colorless oil in 50% (0.45 g) yield. IR (KBr pellet, cm^{-1}): 3400, 1615, 1112. FAB MS *m*/*z* (M^+) calcd 324.3, found 324.0. Anal. Calcd for $C_{20}H_{20}O_4$: C, 74.06; H, 6.21. Found: C, 74.09; H, 6.20.

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Supporting Information Available: Additional UV/vis, fluorescence, and NMR spectra, as well as calculation data. This material is available free of charge via the Internet at http://pubs.acs.org.

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