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Bidirectional Photoinduced Electron-Transfer Quenching Is Observed in 4-Amino-1,8-naphthalimide-Based Fluorescent Anion Sensors

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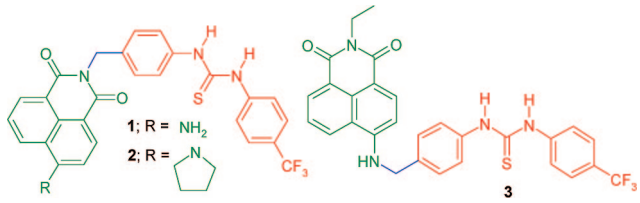
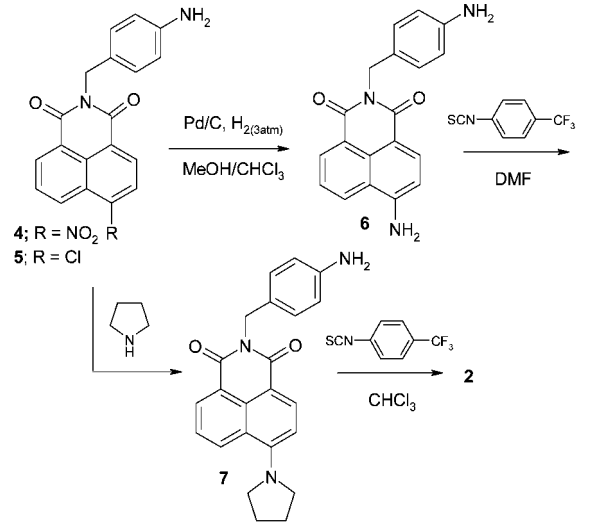


The synthesis and photophysical evaluations of two new fluorescent photoinduced electron-transfer (PET) anion sensors, **1** and **2**, is described. These are based on 4-amino-1,8-naphthalimide fluorophores and diarylthiourea anion receptors, connected via a methylene spacer to the imide. The sensing of acetate, phosphate, and fluoride, on all occasions, gave rise to quenching in the fluorescence of **1** and **2**, similar to that seen for the structural isomer **3**. These results demonstrate that bidirectional PET sensing occurs in such naphthalimide-based anion sensors.

The sensing of anions, through the modulation of ground- or excited-state changes, has become a very active area of reserch in recent times within the field of supramolecular chemistry.[1−7] Of the many examples developed to date, the internal charge transfer (ICT) excited state based 4-amino-1,8-naphthalimide (Naph) chromophore has been a popular choice in such sensors.[8,9] This is because it strongly absorbs and emits at long wavelengths, features that are highly desirable for sensing in competitive media.[9] In particular, the Naph have been exploited in the design of *fluorophore−spacer−receptor*-based photoinduced electron-transfer (PET) sensors.[1,9] Indeed, we have recently demonstrated its use in the fluorescent PET sensing of Zn(II)[10] as well as in the colorimetric sensing of anions.[1,11] In all these cases, the receptors were connected to the Naph moiety at the 4-position. This is due to the "*push−pull*" nature of the ICT excited state of Naph (caused by the electron-donating amine and the electron-withdrawing imide), which gives rise to a charge-separated excited state. This favors PET quenching of the Naph excited state by electron-rich receptors located at the 4-postion. For this reason, PET quenching from receptors connected via the imide moiety is normally prevented.[12−14] Hence, directional PET quenching occurs in such Naph structures, in a similar manner to that seen for the photosynthetic reaction center. This was first proposed, and demonstrated, by de Silva and Rice in 1996.[12a] By using several structural isomers of pH-based Naph PET sensors (using tertiary amines as receptors), they showed that the Naph emission was only "*switched on*" when the H^+ receptors were connected at the 4-amino moiety.[12a] The theoretical examination for this directionality was subsequently investigated by Marcus et al.[13] who concluded that this directionality was "due to the difference in the electronic coupling matrix elements ($|V|$) for the two reactions" and that the electron transfer from the 4-amino side was $\sim 10^4$ times faster than from the imide side. Such directionality has also been investigated by Qian et al.[14a] and Tian et al.[14b] using Naph-based pH PET sensors.

SCHEME 1. Synthesis of the PET Anion Sensors 1 and 2



In 2003, we demonstrated, for the first time, the use of the Naph in PET sensors for anions and that deprotonation could also occur in competition, or in conjunction, with such hydrogen bonding.[15] Based on aryl thioureas as a hydrogen-bonding receptor, connected to the Naph at the 4-amino moiety via a CH_2 spacer, we developed sensors such as **3**. We showed that the excited-state of Naph was indeed quenched upon anion recognition, as the ΔG_{ET} became more thermodynamically favorable upon binding of anions at the thiourea receptor.[16] Herein, we demonstrate that such anion sensing is also possible in the PET sensors **1** and **2**, the structural isomers of **3**. We propose that in the case of **1** and **2**, such an effect is due to an enhanced electron-charge density at the receptor site upon anion sensing, which allows PET to occur from the receptor to the Naph excited state. To the best of our knowledge, **1**−**3** are the first examples of Naph-based anion sensors that give rise to such *bidirectional PET quenching*.

(1) (a) Gunnlaugsson, T.; Glynn, M; Tocci (née Hussey) , G. M.; Kruger, P. E.; Pfeffer, F. M *Coord. Chem. Rev.* **2006**, *250*, 3094. (b) Gunnlaugsson, T.; Ali, H. D. P.; Glynn, M.; Kruger, P. E.; Hussey, G. M; Pfeffer, F. M.; dos Santos, C. M. G.; Tierney, J.; *J. Fluoresc.* **2005**, *15*, 287.

(2) Sessler, J. L.; Gale, P. A.; Cho, W. S. *Anion Receptor Chemistry*; Royal Society of Chemistry: Cambridge, UK, 2006.

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The synthesis of **1** and **2** is shown in Scheme 1. The starting material **4** (see the Supporting Information), which yielded **1**, was formed by reacting first 4-aminobenzylamine with 4-nitro-1,8-naphthalic anhydride in EtOH in 90% yield. Catalytic hydrogenation of **4**, using 3 atm of H_2 pressure, in the presence of 10% Pd/C catalyst for 24 h, gave the diamine **6** in 86% yield. In a similar manner, compound **5** (see the Supporting Information), which yielded **2**, was formed from 4-chloro-1,8-naphthalic anhydride in 70% yield. Subsequent reaction in neat pyrrolidine, under reflux for 18 h, gave **7** after aqueous workup in 71% yield. The two sensors **1** and **2** were then formed from **6** and **7**, respectively, by treating these intermediates with 4-(trifluoromethyl)phenyl isothiocyanate in DMF and $CHCl_3$, respectively, by stirring at room temperature for 5 days under an atmosphere of argon. The resulting precipitate was collected by suction filtration and washed with cold $CHCl_3$ and, in the case of **2**, also by purification using column chromatography on flash silica (gradient elution CH_2Cl_2/MeOH 0 → 98:2). This gave **1** and **2** in 78 and 72% yields, respectively, as highly colored powders. Both sensors showed characteristic resonances in their ^{1}H NMR (400 MHz, DMSO-d_6; See Figures S1 and S2 (Supporting Information) for **1** and **2**) spectra for the thiourea protons, the Naph moiety, and for **1**, the 4-amino protons (see Figure S3 (Supporting Information) for compounds **4**−**7**).

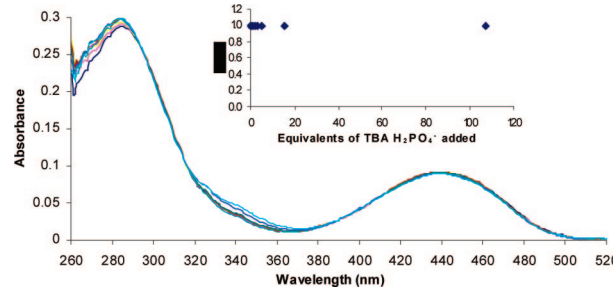

FIGURE 1. Changes in the absorption spectra of **1** (18 μM) upon titration with $H_2PO_4^-$ (TBA) in DMSO (0 → 44 mM). Inset: The relative changes in the ICT band at 438 nm.

The photophysical properties of **1** and **2** were evaluated in DMSO solution. The absorption spectra of both sensors showed the presence of the ICT band of Naph, with λ_{max} at 438 nm ($\log \epsilon = 5.19\ M^{-1}cm^{-1}$) and 454 nm ($\log \epsilon = 15.30\ M^{-1}\ cm^{-1}$), for **1** and **2**, respectively. For both, a second band also appeared at higher energy (centered at ca. 285 nm), assigned to their corresponding $\pi-\pi^*$ transitions.

An "ideal" PET sensor should not display changes in its absorption spectra of the fluorophore upon recognition at the receptor site.[7,10,15] Indeed, this was found to be the case for **1** and **2** upon titration with anions such as AcO^- and $H_2PO_4^-$ (as their tetrabutylammonium salt solutions). This is demonstrated in Figure 1, for **1**, upon titration with $H_2PO_4^-$, where no significant changes were observed up to 100 equiv of the anion (see Figure S4, Supporting Information). However, some changes were observed in the absorption window of 320 − 360 nm, which were assigned to the diarylthiourea receptor. These signified the formation of a hydrogen bonding complex between the anion and the thiourea protons in the ground state.[8a,14,15] Similarly, for AcO^- (see Figures S5 and S6, Supporting Information), Cl^-, and Br^-, no significant changes were observed in the structure of the ICT band. However, in the case of F^-, significant changes were seen in the ICT band of **1** at high concentration of F^-, where a long wavelength absorption band was observed at 529 nm and a second transition developed at 332 nm, with concomitant isosbestic points at 476 and 300 nm, respectively, Figure 2. These results are in agreement with that previously observed for **3**, where at a high concentration of F^- deprotonation of the 4-amino moiety,[8a] with concomitant changes in the absorption spectra, and the formation of HF_2^- occurred.[1,14,18] Importantly, these spectral changes were reversed upon addition of competitive hydrogen-bonding solvents, e.g., MeOH (see later). In contrast, such changes were *not* seen in the ICT band of **2**, which lacks the 4-amino protons (Figure S7, Supporting Information).

The changes in the fluorescence emission of **1** and **2** were next investigated. Excitation of their ICT absorption bands gave rise to long wavelength emission, centered at 528 and 533 nm for **1** and **2**, respectively. The fluorescence quantum yield (Φ_F) for **1** was determined as 0.41, while for compound **2**, it was significantly reduced to $\Phi_F = 0.01$. This reflects the effect that the bulkier 4-amino tertiary amine has on the excited-state

(3) (a) Gale, P. A.; Garcia-Garrido, S. E.; Garric, J. *Chem. Soc. Rev.* **2008**, *37*, 151. (b) Padros, P.; Quesada, R. *Supramol. Chem.* **2008**, *20*, 201. (c) Gale, P. A. *Acc. Chem. Res.* **2006**, *39*, 465. (d) Gale, A. P.; Quesada, R. *Coord. Chem. Rev.* **2006**, *250*, 3219. (e) Amendola, V; Esteban-Gomez, D; Fabbrizzi, L; Liechelli, M. *Acc. Chem. Res.* **2006**, *44*, 8690. (f) Steed, J. W. *Chem. Commun.* **2006**, 2637. (g) Katayev, E. A.; Ustynyuk, Y. A; Sessler, J. L *Coord. Chem. Rev.* **2006**, *250*, 3004. (h) O'Neil, E. J.; Smith, B. D. *Coord. Chem. Rev.* **2006**, *250*, 3068. (i) Nguyen, B. T.; Anslyn, E. V. *Coord. Chem. Rev.* **2006**, *250*, 3118. (j) Lavigne, J. J.; Anslyn, E. V. *Angew. Chem., Int. Ed.* **2001**, *40*, 3118.

(4) (a) Hu, S.; Guo, Y.; Xu, J.; Shao, S. *Org. Biomol. Chem.* **2008**, *6*, 2071. (b) Dos Santos, C. M. G.; Glynn, M.; McCabe, T.; De Melo, J. S. S.; Burrows, H. D; Gunnlaugsson, T. *Supramol. Chem.* **2008**, *20*, 407. (c) Liu, W.-X.; Jiang, Y.-B. *Org. Biomol. Chem.* **2007**, *5*, 1771. (d) Pfeffer, F. M.; Seter, M.; Lewcenko, N.; Barnett, N. W. *Tetrahedron Lett.* **2006**, *47*, 5251. (e) Beer, P. D.; Sambrook, M. R.; Curiel, D. *Chem. Commun.* **2006**, 2105. (f) Wu, F. Y.; Li, Z.; Guo, L.; Wang, X.; Lin, M. H.; Zhao, Y. F.; Jiang, Y. B. *Org. Biomol. Chem.* **2006**, *4*, 624. (g) Ghosh, K.; Adhikari, S. *Tetrahedron Lett.* **2006**, *47*, 8165. (h) Tomasulo, M.; Raymo, F. M. *Org. Lett.* **2005**, *7*, 4633. (i) Nishiyabu, R.; Anzenbacher, P., Jr. *J. Am. Chem. Soc.* **2005**, *127*, 8270.

(5) (a) Lowe, A. J.; Dyson, G. A.; Pfeffer, F. M. *Eur. J. Org. Chem.* **2008**, 1559. (b) Callan, J. F.; Mulrooney, R. C.; Kamila, S.; McCaughan, B. *J. Fluoresc.* **2008**, *18*, 527. (c) Yang, R.; Liu, W.-X.; Shen, H.; Huang, H.-H.; Jiang, Y.-B. *J. Phys. Chem. B* **2008**, *112*, 5105. (d) Filby, M. H.; Dickson, S. J.; Zaccheroni, N.; L.; Prodi, Bonacchi, S.; Montalti, M.; Paterson, M. J.; Humphries, T. D.; Chiorboli, C.; Steed, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 4105. (e) Lowe, A. J; Dyson, F. A; Pfeffer, F. M. *Org. Biomol. Chem.* **2007**, *5*, 1343.

(6) (a) Quinlan, E.; Matthews, S. E.; Gunnlaugsson, T. *J. Org. Chem.* **2007**, *72*, 7497. (b) Pfeffer, F. M.; Kruger, P. E.; Gunnlaugsson, T. *Org. Biomol. Chem.* **2007**, *5*, 1894. (c) Pfeffer, F. M.; Gunnlaugsson, T.; Jensen, P.; Kruger, P. E. *Org. Lett.* **2005**, *7*, 5375. (d) Quinlan, E.; Matthews, S. E.; Gunnlaugsson, T. *Tetrahedron Lett.* **2006**, *47*, 9333.

(7) (a) Davis, A. P.; O'Brien, J. E.; Glynn, M. *Org. Biomol. Chem.* **2005**, *3*, 48. (b) Gunnlaugsson, T.; Davis, A. P.; Hussey, G. M.; Tierney, J.; Glynn, M. *Org. Biomol. Chem.* **2004**, *2*, 1856. (c) Gunnlaugsson, T.; Davis, A. P.; O'Brien, J. E.; Glynn, M. *Org. Lett.* **2002**, *4*, 2449.

(8) (a) Duke, R. M.; Gunnlaugsson, T. *Tetrahedron Lett.* **2007**, *48*, 8043. (b) Xu, Z; Kim, S; Kim, H. N.; Han, S. J.; Lee, C.; Kim, J. S.; Qian, X. H.; Yoon, J. *Tetrahedron, Lett.* **2007**, *48*, 9151. (c) Li, Y.; Cao, L. F.; Tian, H. *J. Org. Chem.* **2006**, *71*, 8279. (d) Esteban-Gomez, D.; Fabbrizzi, L.; Liechelli, M. *J. Org. Chem.* **2005**, *70*, 5717. (e) Liu, B; Tian, H. *Chem. Lett.* **2005**, *34*, 606. (f) Liu, B; Tian, H. *J. Mater. Chem.* **2005**, *15*, 2681.

(9) (a) Callan, J. F.; de Silva, A. P.; Magri, D. C. *Tetrahedron,* **2005**, *61*, 8551. (b) de Silva, A. P.; Gunaratne, H. Q. N.; Gunnlaugsson, T.; Huxley, A. J. M.; McCoy, C. P.; Rademacher, J. T.; Rice, T. E. *Chem. Rev.* **1997**, *97*, 1515.

(10) Parkesh, R.; Lee, T. C.; Gunnlaugsson, T. *Org. Biomol. Chem.* **2007**, *5*, 310.

(11) Gunnlaugsson, T.; Kruger, P. E.; Jensen, P.; Tierney, J; Ali, H. D. P.; Hussey, G. M *J. Org. Chem.* **2005**, *70*, 10875.

(12) (a) de Silva, A. P.; Rice, T. E. *Chem. Commun.* **1999**, 163. (b) See also: de Silva, A. P.; Goligher, A.; Gunaratne, H. Q. N.; Rice, T. E. *Arkivoc* **2003**, *7*, 229.

(13) Gao, Y. Q.; Marcus, R. A *J. Phys. Chem. A* **2002**, *106*, 1956.

(14) (a) Xiao, Y.; Fu, M.; Qian, Z.; Cui, J. *Tetrahedron Lett.* **2005**, *46*, 6289. (b) Tian, H.; Xu, T.; Zhao, Y.; Chen, K. *J. Chem. Soc., Perkin Trans. 2* **1999**, 545.

(15) Gunnlaugsson, T.; Kruger, P. E.; Lee, T. C.; Parkesh, R.; Pfeffer, F. M.; Hussey, G. M. *Tetrahedron Lett.* **2003**, *44*, 6575.

(16) Gunnlaugsson, T.; Davis, A. P.; Glynn, M. *Chem. Commun.* **2001**, 2556.

(17) Saha, S.; Samanta, A. J. *Phys. Chem. A* **2002**, *106*, 4763.

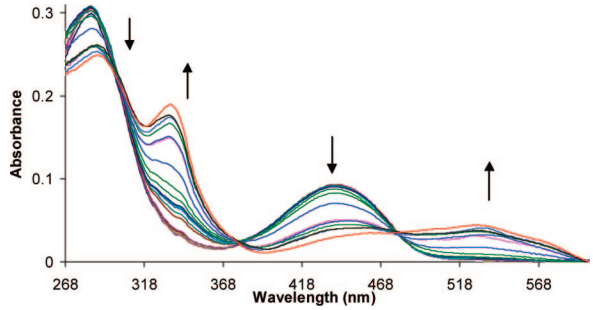

FIGURE 2. Changes in the absorption spectra of **1** (18 μM) upon titration with F^- (TBA) in DMSO (0 → 32 mM).

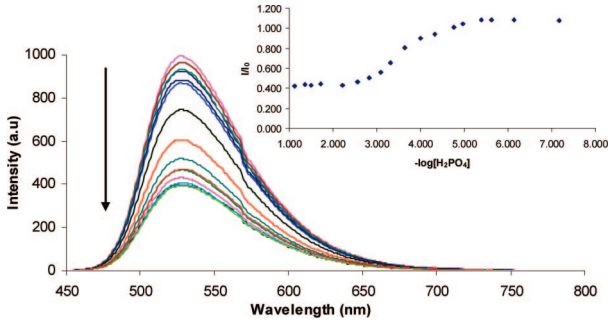

FIGURE 3. Changes in the fluorescence emission spectra of **1** (18 μM) upon titration with $H_2PO_4^-$ (TBA) in DMSO (0 → 44 mM). Inset: The relative changes at 528 nm as a function of $-\log [H_2PO_4^-]$.

properties of **2**.[17] In our previous study, **3** was found to have $\Phi_F = 0.71$.[15] While this difference in quantum yield between **3** and **1** is not considerable (ca. a factor of 2), it clearly indicates that the excited state of **1** is quenched, most likely by PET from the receptor moiety. This would suggest that bidirectional electron transfer should be allowed in the structural isomers **1** and **2** in a similar manner to that observed for **3**.

To investigate this, we carried out fluorescence titrations using various anions capable of binding to the thiourea receptor moiety via linear "Y-type" bonding interactions, with concomitant high binding affinities.[18] Upon titration with $H_2PO_4^-$ and AcO^- (Figure S8, Supporting Information) significant changes were indeed observed in the fluorescence emission spectra of Naph. For $H_2PO_4^-$, Figure 3, the fluorescence emission was quenched by ca. 60% at the end point. This quenching is of similar magnitude as was observed for **3** under identical conditions.[15] Moreover, no significant shifts were observed in λ_{max} for **1**. The changes in the ICT band at 532 nm as a function of $-\log [H_2PO_4^-]$ are shown in the inset in Figure 3 and demonstrate typical sigmoidal behavior, which is classically observed for 1:1 binding in PET sensors.[7,9,10] Upon addition of competitive hydrogen-bonding solvents such as MeOH, the emission was "switched on", demonstrating the reversibility for the anion recognition at the thiourea receptor (Figure S9, Supporting Information, for $H_2PO_4^-$). Furthermore, since no significant changes were observed in the absorption spectra (Figure 1), then these results clearly demonstrate that PET is active upon anion recognition in **1** and that this new design *enables bidirectional PET quenching* in such Naph based anion sensors. In a similar manner, for **2**, the Naph fluorescence emission was also

(18) (a) Lowe, A. J.; Pfeffer, F. M. *Chem. Commun.* **2008**, 1871. (b) Dos Santos, C, M.; G.; McCabe, T.; Gunnlaugsson, T. *Tetrahedron Lett.* **2007**, *48*, 3135. (c) Evans, L. S.; Gal, e, P. A.; Light, M. E.; Quesada, R. *Chem. Commun.* **2006**, 965. (d) Gunnlaugsson, T.; Kruger, P. E.; Jensen, P.; Pfeffer, F. M.; Hussey, G. M. *Tetrahedron Lett.* **2003**, *44*, 8909.

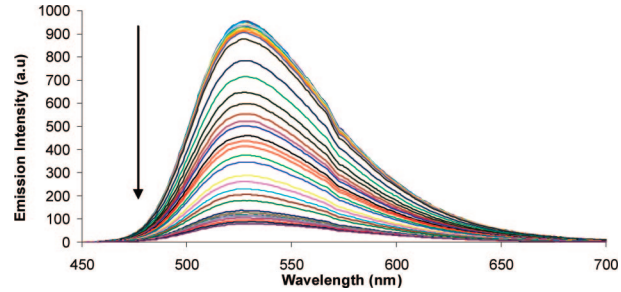

FIGURE 4. Changes in the fluorescence emission spectra of **1** (15 μM) upon titration with F^- (TBA) in DMSO (0 → 32 mM).

quenched for $H_2PO_4^-$, but to a lesser extent (Figure S10, Supporting Information).

To further explore this phenomenon, **1** (Figure 4) and **2** (Figure S11, Supporting Information) were titrated with F^-, which is known to bind strongly to (or lead to deprotonation of)[18] thiourea-based anion receptors.[8a,18] Indeed, a very effective quenching (ca. 90%) was observed, with no changes in λ_{max}. This further demonstrates the efficiency of PET from the receptor; prompted by the anion recognition event. The use of HO^-, which should lead to deprotonation of the thiourea moiety and hence produce a highly electron-rich "receptor", also gave rise to efficient quenching (Figure S12, Supporting Information). For **2**, the titration of F^- also quenched the excited state, but to a lesser extent than seen for **1** (ca. 50%,).

To quantify the above changes in the Naph emission of **1** and **2**, we analyzed the emission changes[19] using the nonliner regression analysis program SPECFIT. The results of these fittings and the corresponding speciation distribution diagrams are shown in the Supporting Information (see Figures S13−23 and Table S1). For **1**, and then in the case of $H_2PO_4^-$ only, the 1:1 stoichiometry was observed, with log β of 3.50 ± 0.03. Similar results, log β of 3.24 ± 0.05, were observed for **2**. Furthermore, these values are similar to that observed for **3**, with log $\beta = 3.1$.[15] In a similar manner, the binding of AcO^- also gave rise to 1:1 binding stoichiometry (other were also determined),[20] with log $\beta = 4.23 \pm 0.02$ and 4.20 ± 0.04 for **1** and **2**, respectively, which suggests that the primary vs tertiary 4-amino substitute does not affect the sensitivity of the anion recognition at the receptor site to a large extent. These are, once more, similar in magnitude to that observed for **3**[15] (Table S2, Supporting Information). Hence, these results clearly demonstrate that the location of the anion receptor does not significantly influence the sensitivity in these structural isomers. Furthermore, the selectivity and the percent of Naph quenching follow the same trend as seen for **3** (Table S2, Supporting Information). Hence, we conclude that provided the electron density of the receptor is sufficient; it will overcome the barrier proposed by de Silva et al.[12] and Marcus at al.,[13] and bidirectional PET quenching becomes allowed. This is an important observation as it permits the development of other supramolecular systems based on our design, where either the 4th or the imide or both positions of the Naph structure can be functionalized with anion receptors.

In summary, the results from our investigation establish that PET quenching of the Naph excited state in **1** and **2** *is observed* upon anion recognition and that the location of the anion

(19) (a) Plush, S. E.; Gunnlaugsson, T. *Org. Lett.* **2007**, *9*, 1919. (b) Harte, A. J.; Jensen, P.; Plush, S. E.; Kruger, P. E.; Gunnlaugsson, T. *Inorg. Chem.* **2006**, *45*, 9465.

receptor does not affect the sensitivity or the selectivity of the anion sensing to a great extent. We are currently exploring these important results in the study of other anion sensing systems based on **1**−**3**.

Experimental Section

6-Amino-2-(4-aminobenzyl)benzo[*de*]isoquinoline-1,3-dione (6). Compound **6** was synthesized by hydrogenating **4** (0.50 g, 4.30 mmol, 1 equiv) in MeOH/DCM (2:1) at 3 atm pressure in the presence of 10% Pd/C catalyst (0.2 equiv) for 24 h. The reaction mixture was then diluted with MeOH, filtered through Celite, and washed with MeOH. The filtrate and washings were evaporated under reduced pressure to yield the product as an orange solid (0.39 g, 86%): mp 287−288 °C; δ_H (400 MHz, $(CD_3)_2SO$) 8.67 (1H, d, J = 8.0 Hz, Ar-H7), 8.44 (1H, d, J = 7.0 Hz, Ar-H2), 8.20 (1H, d, J = 8.5 Hz, Ar-H5), 7.66 (1H, t, J = 8.0 Hz, Ar-H6), 7.57 (2H, br s, NH_2), 7.34 (2H, d, J = 8.0 Hz, Ar-H2′, Ar-H5′), 7.10 (2H, d, J = 8.0 Hz, Ar-H3′, Ar-H4′), 6.87 (1H, d, J = 8.0 Hz, Ar-H3), 5.18 (2H, s, CH_2); δ_C (100 MHz, $(CD_3)_2SO$) 164.3, 163.3, 153.5, 135.1, 134.7, 131.7, 130.3, 130.1, 129.2, 124.5, 122.0, 121.1, 119.8, 108.7, 107.6, 42.5; m/z 318 $(M + H)^+$, 340 $(M + Na)^+$; ν_{max} (neat sample)/cm^{-1} 3318, 3182, 1674, 1570. Anal. Calcd for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24. Found: C, 71.61; H, 4.79; N, 13.54.

2-(4-Aminobenzyl)-6-pyrrolidin-1-ylbenzo[*de*]isoquinoline-1,3-dione (7). Compound **7** was synthesized by treating **5** (0.30 g, 0.89 mmol) with pyrrolidine (3.4 g, 4 mL, 56.1 mmol) and stirring the reaction mixture at reflux temperature for 18 h. The reaction mixture was then filtered hot through Celite, and the filtrate was poured immediately into ice-cold water and stirred for 1 h. The resulting precipitate was then collected by suction filtration, washed with ice-cold water, and dried over BaO to yield the product as a red/brown solid (0.234 g, 71%) after recrystallization from EtOH and subsequent purification by dry column chromatography on flash silica (DCM/MeOH 0 → 2%): mp 175−177 °C; HRMS 394.1541 ($[M + Na]^+$, $C_{23}H_{21}N_3O_2$ requires 394.1531); δ_H (400 MHz, $CDCl_3$) 8.57 (2H, d, J = 7.0 Hz, Ar-H7, Ar-H2), 8.43 (1H, d, J = 8.5 Hz, Ar-H5), 7.52 (1H, t, J = 7.5 Hz, Ar-H6), 7.42 (2H, d, J = 8.0 Hz, Ar-H2′, Ar-H5′), 6.80 (1H, d, J = 8.5 Hz, Ar-H3), 6.63 (2H, d, J = 8.0 Hz, Ar-H3′, Ar-H4′), 5.30 (2H, s, CH_2), 4.28 (4H, s, CH_2), 2.10 (4H, s, CH_2); δ_C (100 MHz, ($CDCl_3$) 164.9, 164.1, 152.6, 145.5, 133.5, 131.9, 131.2, 131.1, 130.5, 128.1, 123.0, 122.6, 122.5, 114.9, 110.8, 108.4, 53.1, 42.8, 26.0; m/z 394 $(M + Na)^+$; ν_{max} (neat sample)/cm^{-1} 3476, 3011, 1654, 1406, 1001. Anal. Calcd for $C_{23}H_{21}N_3O_2$: C, 74.37; H, 5.70; N, 4.31. Found: C, 74.07; H, 5.50; N, 4.21.

1-[4-(6-Amino-1,3-dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-ylmethyl)phenyl]-3-*p*-tolylthiourea (1). Compound **1** was synthesized by treating **6** (0.1 g, 0.315 mmol, 1 equiv) with 4-(trifluoromethyl)phenyl isothiocyanate (0.06 g, 0.315 mmol, 1 equiv) in DMF and stirring the reaction mixture at rt for 5 days under argon. The solvent was reduced in volume azeotropically with toluene under reduced pressure, and the product was then precipitated into water, collected by suction filtration, and dried. The product was then dissolved in DCM and washed with water (×3) and brine, and the organic layer was dried over $MgSO_4$, filtered, and evaporated to dryness to yield **1** as a yellow solid (0.11 g, 78%) after recrystallization from EtOH: mp 178−179 °C; δ_H (400 MHz, $(CD_3)_2SO$) 10.0 (2H, s, NH × 2), 8.61 (1H, d, J = 8.5 Hz, Ar-H7), 8.44 (1H, d, J = 7.0 Hz, Ar-H2), 8.20 (1H, d, J = 8.5 Hz, Ar-H5), 7.71 and 7.63 (5H, m, Ar-H6, Ar-H2′, Ar-H6′ and Ar-H3′, Ar-H5′), 7.49 (2H, s, NH_2), 7.35 (2H, d, J = 8.5 Hz, Ar-H9′, Ar-H11′), 7.30 (2H, d, J = 8.5 Hz, Ar-H8′, Ar-H12′), 6.86 (1H, d, J = 8.0 Hz, Ar-H3), 5.18 (2H, s, CH_2); δ_C (100 MHz, $(CD_3)_2SO$),180.0, 164.3, 163.3, 153.4, 143.9, 138.3, 134.9, 134.7, 131.7, 130.2, 130.0, 128.3, 125.9, 124.5, 124.2, 123.4, 123.2, 122.1, 119.8, 108.7, 107.7, 42.5; m/z 467 $(M + H)^+$; ν_{max} (neat sample)/cm^{-1} 3235, 2924, 1629, 1318, 1100, 1065. Anal. Calcd for $C_{27}H_{22}N_4O_2S$: C, 69.51; H, 4.75; N, 12.01. Found: C, 69.21; H, 4.50; N, 11.81.

1-[4-(1,3-Dioxo-6-pyrrolidin-1-yl-1*H*,3*H*-benzo[*de*]isoquinolin-2-ylmethyl)phenyl]-3-*p*-tolylthiourea (2). Compound **2** was synthesized by treating **7** (0.099 g, 0.267 mmol, 1 equiv) with 4-(trifluoromethyl)phenyl isothiocyanate (0.054 g, 0.267 mmol, 1 equiv) in $CHCl_3$ and stirring the reaction mixture at rt for 5 days under argon. The resulting precipitate was collected by suction filtration and washed with $CHCl_3$ to yield the product as a red solid (0.1 g, 72%) after purification by recrystallization from EtOH followed by column chromatography on flash silica (gradient elution DCM/MeOH 0 → 2%): mp 158 − 159 °C; δ_H (400 MHz, $CDCl_3$), 8.62 (1H, d, J = 8.5 Hz, Ar-H7), 8.59 (1H, d, J = 7.5 Hz, Ar-H2), 8.43 (1H, d, J = 9.0 Hz, Ar-H5), 8.0 (1H, br s, NH), 7.78 (1H, br s, NH), 7.64 and 7.54 (8H, m, Ar-H) 7.26 (1H, d, J = 8.0 Hz, Ar-H6), 6.82 (1H, d, J = 8.5 Hz, Ar-H3), 5.39 (2H, s, CH_2), 3.82 (4H, s, CH_2), 2.13 (4H, s, CH_2); δ_C (100 MHz, $CDCl_3$), 179.6, 164.9, 164.0, 152.9, 141.3, 137.4, 135.2, 133.8, 132.4, 1314, 131.3, 130.2, 125.9, 125.8, 125.3, 124.1, 123.0, 122.4, 122.1, 109.8, 108.5, 53.2, 42.8, 26.0; m/z 543 $(M + Na)^+$; ν_{max} (neat sample)/cm^{-1} 2968, 1678, 1304, 1108, 1064, 1015. Anal. Calcd for $C_{31}H_{28}N_4O_2S$: C, 71.51; H, 5.42; N, 10.76. Found: C, 71.21; H, 5.52; N, 10.51.

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Supporting Information Available: Synthesis and characterization of **4**−**7**, Figures S1−S21, and Tables S1 and S2. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) For both **1** and **2**, a second binding interaction was also observed at higher anion concentration (Table S1 for details). The fitting for F^-, for both **1** and **2**, also gave rise to 1:1 and 1:2 binding interactions, signifying the deprotonation of the thiourea moiety. These changes mirrored that observed for **3** (ref 15). It was difficult to obtain reliable binding constants from the fitting of **2** for F^-, most likely due to concomitant deprotonation events.