ORGANIC
LETTERS

2004
Vol. 6, No. 20
3445−3448

Efficient and Simple Colorimetric Fluoride Ion Sensor Based on Receptors Having Urea and Thiourea Binding Sites†

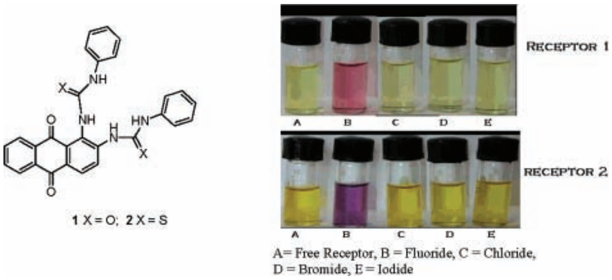
D. Amilan Jose, D. Krishna Kumar, Bishwajit Ganguly,* and Amitava Das*

Central Salt and Marine Chemicals Research Institute,
Bhavnagar: 364002, Gujarat, India

amitavaad1@sancharnet.in; salt@csir.res.in

Received June 21, 2004

ABSTRACT



Novel colorimetric receptors for selective fluoride ion sensing containing anthraquinone as chromogenic signaling subunit and urea (*N,N′′*-(9,10-dihydro-9,10-dioxo-1,2-anthracenediyl)bis[*N′*-phenyl])/thiourea (*N,N′′*-(9,10-dihydro-9,10-dihydro-9,10-dioxo-1,2-antrhacenediyl)bis[*N*-phenyl]) binding sites have been reported. These receptors have shown no affinity for other halide ions (Cl^-, Br^-, and I^- ions). Well-defined color change in the visible region of the spectrum was observed upon addition of fluoride ion in DMSO/CH_3CN solution of the receptors 1 and 2.

The search of a chemosensor for recognition and sensing of specific anionic analytes is emerging as a research area of considerable importance.[1] In particular, the development of colorimetric anion sensing is even more important and increasingly appreciated since naked eye detection can offer qualitative and quantitative information.[1,2] However, examples in general, for the sensitive and simple-to-use colorimetric anion sensors are rather limited compared to the fluorescence-based ones.[2,3]

Among various important anionic analytes, biologically important fluoride ion is one of the most significant due to its role in dental care and treatment of osteoporosis.[4] Many examples are available on selective fluorescent photoelectron transfer (PET) receptor molecules for fluoride ion.[3,5] There is paucity of reports that describe the change in color in the visible region of the spectrum and thereby allow the naked eye detection for fluoride ion.[6] Reports in this regard are mostly restricted to the use of calix[4]pyrrole or its derivative, dipyrrolylquinoxalines and 1,2-diaminoanthraquinone.[6,7] The binding constant reported for the fluoride ion with dipyrrolylquinoxalines is relatively larger; however, for other

---

† Authors would like to dedicate this paper to the memory of Prof. Bhaskar. G. Maiya.

(1) (a) Gale, P. A. *Coord. Chem. Rev.* **2001**, *213*, 79−128. (b) Sessler, J. L.; Davis, J. M. *Acc. Chem. Res.* **2001**, *34*, 989−997. (c) Beer, P. D.; Gale, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 486−516. (d) Schmidtchen, F. P.; Bergeer, M. *Chem. Rev.* **1997**, *97*, 1609−1646. (e) de Silva, A. P., Gunaratne, H. Q. N.; Gunnlaugsson, T.; Hauxley, A. J. M.; McCoy, C. P., Rademacher, J. T.; Rice, T. E. *Chem. Rev.* **1997**, *97*, 1515−1566.

(2) (a) Suksai, C.; Tuntulani, T. *Chem. Soc. Rev.* **2003**, *32*, 192−202. (b) Sancenon, F.; Descalzo, A. B.; Manez, R. M.; Miranda, M. A.; Soto, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 2640−2643. (c) Lee, D. H.; Lee, H. Y.; Hong, J.-Ju. *Tetrahedron Lett.* **2002**, *43*, 7273−7276. (d) Miyaji, H.; Sato, W.; Sessler, J. L. *Angew. Chem., Int. Ed.* **2000**, *39*, 1777−1780. (e) Starnes, S. D.; Arungundram, S.; Saunders: C. H. *Tetrahedron Lett*, **2002**, *43*, 7785−7788. (f) Zhou, L. L.; Sun, H.; Li, H.-P.; Wang, H.; Zhang, X.-H.; Wu, S.-K.; Lee, S.-T. *Org. Lett.* **2004**, *6*, 1071−1074. (g) D. H. Lee, K. H. Lee, J-I. Hong. *Org. Lett.* **2001**, *3*, 5−8.

(3) (a) Xu., G.; Tarr, M. *Chem. Commun.* **2004**, 9, 1050−1051 and references therein. (b) Sole, S.; Gabbai, F. P. *Chem. Commun.* **2004**, *11*, 1284−1285 and references therein.

(4) (a) Krik, K. L. *Biochemistry of Halogens and Inorganic Halides*; Plenum Press: New York, 1991; p 59l. (b) Kleerekoper, M.; *Endocrinol Metab. Clin. North Am.* **1998**, *27*, 441.

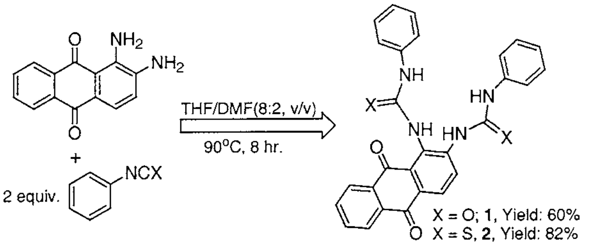
10.1021/ol048829w CCC: $27.50

receptors it is generally moderate and is of the order of 10^3. Despite considerable efforts, attempts to increase the receptor's inherent affinity along with its specificity for fluoride ion has generally led to complexity of design and synthesis. Thus, a challenge remains for chemists to make a colorimetric sensor that is specific and sensitive and has a high association constant for fluoride ion, crucial factors for the design of a simple-to-use detection tool.

One of the reports on the bis-urea functionality based fluorosensor (1,8-bis(*N*-phenylureido)naphthalene) for fluoride ion describes a shift in λ_{max} (from 315 to 370 nm) in the UV region of the electronic spectra on fluoride ion binding.[5a,b] The association constant value (K_f) for this anion, is found to be $\sim 10^5$, and more importantly the selectivity for F^- has been found to be 340 times greater than that for Cl^-. Similar studies with an analogous derivative derived from 1,8-anthracenedimethylamine reveal that K_f for fluoride ion binding is 7.12×10^5, while the selectivity compared to Cl^- is only 120.[5h] Closer examination into the structural aspect of these two derivatives led us to presume that the larger separation distance between the two urea functionality accounts for the observed decrease in selectivity in the latter case. One earlier report describes the use of 1,5-diaminoanthraquinone for synthesis of corresponding urea and thiourea derivatives for use as a colorimetric sensor for various anions, including fluoride ion.[7c] However, no details such as association constant and comparison with the existing sensors are provided. With this information available in the literature, we decided to design a new sensor having an anthraquinone moiety as the colorimetric reporter group and with an appropriate distance between the two urea functionalities to achieve a higher association constant.

Chromogenic sensor **1** (urea, *N,N''*-(9,10-dihydro-9,10-dioxo-1,2-anthracenediyl)bis[*N'*-phenyl]) was synthesized following the methodology shown in (Scheme 1) and isolated as a pure compound in a reasonably good yield (60%). Receptor **2** (thiourea, *N,N''*-(9,10-dihydro-9,10-dioxo-1,2-anthracenediyl)bis[*N'*-phenyl]) was synthesized using phenylisothiocyanate instead of phenylisocyanate (Scheme 1). Other synthetic methodologies are identical; however, the yield for receptor **2** was higher (82%). ^{1}H NMR spectroscopy and elemental analysis data for receptors (**1** and **2**) match with their proposed formulation. UV−vis spectra of **1** and **2** in DMSO/CH_3CN (1:9, v/v) showed λ_{max} at 422 nm (ϵ = 8160 M^{-1} cm^{-1}) and 459 nm (ϵ = 18680 M^{-1} cm^{-1}), respectively. Preliminary titration experiments for fluoride ion with receptor **1** did not show any color change even when allowed to stand at room temperature for more than 24 h. However, the color of the DMSO/CH_3CN (1:9, v/v) solution changes, in the presence of fluoride ion, to pale red when the temperature of the mixture was systematically raised from rt to 60 °C; λ_{max} at 422 nm for **1** disappears, while a new λ_{max} at 530 nm (ϵ = 8500 M^{-1} cm^{-1}) with two isosbestic points at 369 and 460 nm appears. Similar experiments with corresponding Cl^-, Br^-, and I^- salts were repeated, and no significant change in spectra was observed, suggesting no binding or very weak binding of those ions to the receptor molecules.

Scheme 1



To examine this behavior of receptor **1**, ab initio quantum chemical calculations were performed. The structure of **1** and **1F**$^-$, **1Cl**$^-$, and **1Br**$^-$ were optimized at the Hartree−Fock RHF/6-31G* level of theory.[8] For computational simplicity, the anthraquinone moiety was modeled with naphthaquinone. The conformation predicted for the receptor **1** has been found to be intramolecularly hydrogen bonded (Figure 1a). The urea functional groups are not properly aligned for binding the guest anions. The intramolecular N−H···O hydrogen bonded distances calculated at HF/6-31G* are 1.893 and 1.918Å, respectively. C−H···O type interactions have also been observed between the benzene hydrogen and the amide carbonyl group (Figure 1a). Therefore, it appears that such a preferred conformation of receptor **1** does not allow the fluoride ion to complex with the N−H donor atoms; hence, energy is required to properly orient the amido functionality for complexation with the former anion. For further examination, we decided to model a thiourea functionality instead of a urea group and optimized the structure of receptor **2** at the HF/6-31G* level. It is known that sulfur atom forms weaker hydrogen bonds, and hence **2** should act as a better receptor for F^- at room temperature.[9] The HF/6-31G*-calculated results suggest that the NH···S hydrogen bond (ca. 2.473 Å) is much longer than that of NH···O bonds in **1** and the thiourea groups are significantly deviated from the phenyl and naphthaquinone ring planes

---

(5) (a) Lee, J. Y.; Cho, E. J.; Mukamel, S.; Nam, K. C. *J. Org. Chem.* **2004**, *69*, 943−950. (b) 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*, 12376−12377. (c) Miyaji, H.; Anzenbacher, P., Jr.; Sessler, J. L.; Bleasdale, E. R.; Gale, P. *Chem. Commun.* **1999**, *17*, 1723−1725. (d) Anzenbacher, P., Jr.; Jursikova, K.; Sessler, J. L. *J. Am. Chem. Soc*. **2000**, *122*, 9350−9352. (e) *J. Am. Chem. Soc*. **2002**, *124*, 8644−8652. (f) Anzenbacher, P., Jr.; Try, A. C.; Miyaji, H. *J. Am. Chem. Soc*. **2000**, *122*, 10268−10272. (g) Miyaji, H.; Sato, W.; Sessler, J. L *Angew. Chem., Int. Ed.* **2000**, *39*, 1777−1780. (h) Kim, S. K.; Yoon, J. *Chem. Commun.* **2002**, 770−771.

(6) (a) Ghosh, T.; Maiya, B. J. *Proc. India Acad. Sci. (Chem. Sci.)* **2004**, *116*, 1−4. (b) Black, C. B.; Andrioletti, B.; Try, A. C.; Ruiperez, C.; Sessler, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 10438−10439. (c) Lavigne, J. J.; Anslyn, E. V. *Angew. Chem., Int. Ed.* **1999**, *38*, 3903. (d) Piatek, P.; Jurezak, J. *Chem. Commun*. **2002**, *20*, 2450−2452.

(7) (a) Black, C. B.; Andrioletti, B.; Try, A. C.; Ruiperez, C.; Sessler, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 10438−10439. (b) *Angew. Chem., Int. Ed.* **2001**, *40*, 154−157. (c) Jimenez, D.; Manez, R. M.; Sancenon F, Soto, J. *Tetrahedron Lett*, **2002**, *43*, 2823−2825. (d) Desai, R. D.; Dalal, S. K.; Parikh, A. R. *J. Inst. Chem. (India)* **1988**, *60*, 133−136.

(8) (a) *TITAN*; Wavefunction, Inc.: Irvine CA. (b) The interaction energy is simply obtained by the energy of the complex subtracted by the sum of energies of constituents. The interaction is very strong due to charged hydrogen bonds; thus, the basis set superposition error (BSSE) is expected to be negligible compared with the magnitude of the total interaction energies.

(9) Zuika I. V.; Bankovski, A. Yu. *Russ. Chem. Rev.* **1973**, *42*, 22−36.

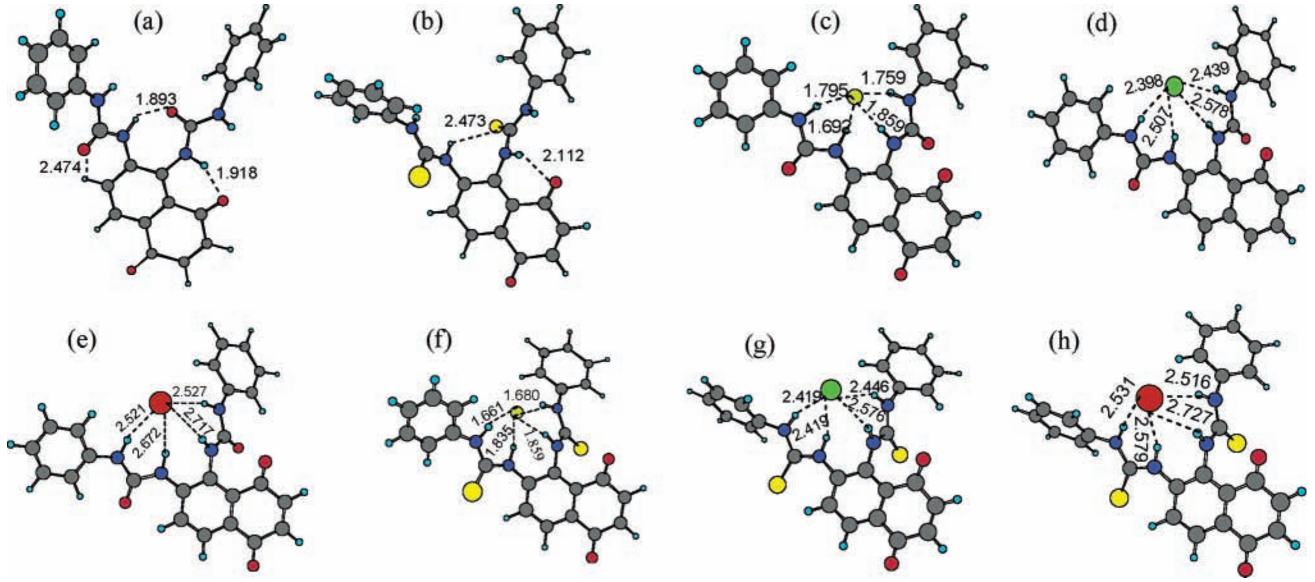


Figure 1. RHF/6-31G*-optimized geometries for the free receptor **1** (a) and its complexes with halides F^- (c), Cl^- (d), and Br^- (e) and for receptor **2** (b) and its complexes with halides F^- (f), Cl^- (g), and Br^- (h) (color key: red = oxygen; blue = nitrogen; yellow = sulfur; greenish-yellow = fluoride; green = chloride; brown = bromide).

(Figure 1b). Consequently, the intramolecular N−H···O hydrogen bond between the naphthaquinone carbonyl group and the donor N−H group becomes longer (2.112 Å) in this case. Therefore, it will be much easier for the receptor **2** to align the thiourea functionality for complex formation with fluoride ion in comparison to receptor **1**. This prompted us to synthesize receptor **2**. To our delight, preliminary titration experiment in a DMSO/CH_3CN (1:9, v/v) solution of receptor **2** with externally added fluoride ion shows an immediate change in color at rt: the color changes from yellow to purple, and the change could be detected by the naked eye. Change in UV−vis spectra for the precise titration of receptor **1** at 60 °C and **2** at rt are shown in Figure 2. Similar experiments performed with receptor **2** and corresponding Cl^-, Br^-, and I^- salts were repeated. For externally added Cl^- and I^- salts, spectra almost remain unchanged, though a little variation was observed with the Br^- salt. These suggest no binding and very little binding of Cl^-/I^- and Br^- ions, respectively, to the receptor molecule **2**.

As seen in Figure 2, a bathochromic shift of 108 and 102 nm was observed on complexation with F^- for receptors **1** and **2**, respectively. λ_{max} of 422 nm for receptor **1** and 459 nm for receptor **2** bleaches on complexation with fluoride ion, and new absorption maxima develop at 530 nm and 561 nm, respectively. Simultaneous growth in absorbance at 310 and 380 nm occurred, while two isobestic points 380 and 500 nm were observed, respectively, for receptors **1** and **2** (Figure 2). Significant bathochromic shift for absorption maxima in the visible region on fluoride ion complexation is presumably due to the charge-transfer interaction between the electron-rich urea/thiourea-bound fluoride ion and the electron-deficient anthraquinone moieties. This also suggests that the excited state would be more stabilized by fluoride ion binding.[1d,2a] Job plots for receptor **1** at 60 °C and receptor **2** at rt with F^- as a guest in a DMSO/CH_3CN (1:9, v/v) solution show maxima at a mole fraction of 0.5 in each case, which signifies that the host binds the anionic guest in a 1:1 ratio. This also indicates that two urea/thiourea groups act as cooperative binding sites.

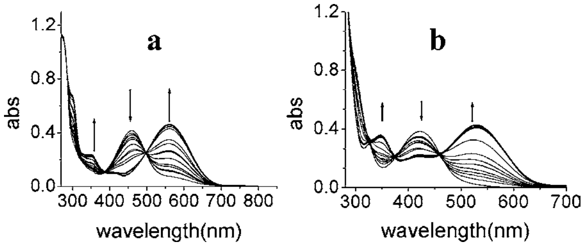


Figure 2. Change in UV−vis spectra for receptor **2** at rt (2.5×10^{-5} M) (a) and receptor **1** at 60 °C (5×10^{-5} M) (b) in DMSO−CH_3CN (1:9, v/v) upon the addition of 7.5×10^{-6} to 5×10^{-4} M of fluoride ion. No further change was observed on addition of even higher concentration of fluoride ion.

The association constant values for receptors **1** and **2** calculated from the UV−vis titration data are summarized in Table 1. Experimental results suggest that receptors **1** and **2** can be termed selective colorimetric sensors for F^-.

The relative preference in binding ability of **1** and **2** for F^- is also evident in ^{1}HNMR titration experiments in DMSO-d_6. A partial ^{1}H NMR spectrum of receptor **2** is shown in (Figure 3), which shows the complete disappearance of the signals for the amide −NH protons upon addition of 5 mol equiv of fluoride ion. A similar observation was reported earlier and is presumably due to strong hydrogen bonding with the fluoride ion.[5a] Signals for −NH protons at 9.719

Table 1.

anion^a	$K_1{}^b$ (M^{-1})	$K_2{}^b$ (M^{-1})
F^-	$(4.4 \pm 0.2)10^5$	$(8.2 \pm 0.5)10^5$
Cl^-		
Br^-		3.4 ± 1.0
I^-		

[a] Tertiary butyl salt of the respective anions were used for the studies. [b] K value reported (K_1 for receptor **1** and K_2 for receptor **2**) is the average of the 11 independent data evaluated from each individual UV−vis titration data for the respective receptor and anion. Confidence limits for the respective K values are also shown.

(1H,S) and 9.795 (1H,S) for **1** at 60 °C and 12.721 (2H,S) and 13.30 (2H,S) for **2** at rt, respectively, disappear on association with the fluoride ion. Such shifts were not observed for Cl^- and I^-, and a small shift was observed when receptor **2** was titrated with Br^- salt solution. The small change in UV−vis spectra for receptor **2** when titrated with different [Br^-] allowed us to evaluate the association constant for Br^- and is summarized in Table 1.

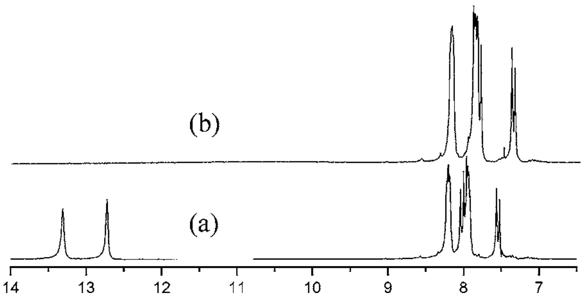


Figure 3. Partial ^{1}H NMR (200 MHz) spectra of receptor **2** in DMSO-d_6 at rt in (a) the absence and (b) the presence of 5.0 equiv of $[(Bu^t)_4N]F$.

The observed selectivity of receptors **1** and **2** for F^- can be explained on the basis of the RHF/6-31G*-optimized structures for the complexes of receptors **1** and **2** with halides (F^-, Cl^-, Br^-) represented in Figure 1. Single-point interaction energies calculated at the B3LYP/6-31G* level using RHF/6-31G*-optimized geometries without basis set superposition error correction are −120.2, −49.0, and −52.9 kcal/mol for F^-, Cl^-, and Br^-, respectively, with receptor **1** and −127.8, −53.1, and −58.1 kcal/mol with receptor **2**.[8b] The large binding energy difference between F^- and Cl^-/Br^- may result in preferential binding for F^- over Cl^-/Br^- in both cases as observed in the titration experiment. The halide ions sit asymmetrically in receptor **1** and **2**, and all four amide/thioamide protons participate in hydrogen bonding with anions (Figure 1c−h). The amido groups prefer to be in the plane of the phenyl rings in receptor **1**; however, the thioamide groups in receptor **2** orient almost perpendicular to the phenyl rings. Upon complexation of halides with receptor **1**, one of the amide units lies in the plane of the phenyl ring, but the other amide group deviates from planarity by ∼18.0°. Interestingly, in the case of receptor **2**, during complexation, one of the thioamide unit moves toward planarity, however, the other one remains perpendicular to the phenyl ring plane. Being smaller in size, fluoride ion approaches much closer to the cavity and interacts much more strongly with the amide/thioamide protons. It is interesting to note that the interatomic distances between the complexed chloride ion and the four amide/thioamide protons are smaller than those of the corresponding bromide ions; however, the binding energy has been found to be marginally preferred for Br^- over Cl^- in receptors **1** and **2** (Figure 1d,e,g,h). The association constant obtained for the complexation of Br^- with receptor **2** supports our calculated results (Table 1). The overall energetic preference for the complexation of Br^- over Cl^- arises presumably due to the lesser electrostatic repulsion between the amido/thioamido group and the naphthaquinone carbonyl group. The calculated torsions at RHF/6-31G* suggest that in the case of Br^-, one of the thioamido groups is oriented more perpendicular with respect to phenyl ring (52.0°) than that of $Cl-$ (55.0°) and hence experiences less electrostatic repulsion in the former case. However, the other thioamido groups are positioned in a similar manner in both cases. Furthermore, the calculated binding energy for the receptor **2** with halides is relatively larger than that of receptor **1**. This result is qualitatively in agreement with the observed association constant for receptors **1** and **2** with fluoride ion (Table 1). It is known that the degree of charge transfer from nitrogen to sulfur in thioamide is significantly greater than that of nitrogen to oxygen in amides, and hence the N−H bonds are better acceptors in the former case.[10] Thus, the anthraquinone moiety acts not only as a spectroscopy receptor group but also as an effective template with an appropriate distance of separation between the urea/thiourea groups for selective binding of the fluoride ion.

In conclusion, we have succeeded in preparing anion sensors that not only allow for the facile colorimetric detection of F^- ion but also are amenable to "color tuning". It has been shown that urea and thiourea binding sites anchored to anthraquinone signaling subunits are suitable colorimetric reagents for F^- sensing. The effect of subtle changes in the structure of the receptor (from urea to thiourea) has been observed. Receptors **1** and **2** have shown little or no affinity for Cl^-, Br^-, and I^- ions. Accordingly, it is possible to conceive the use of these systems in various sensing applications as well as in other situations such as anion transport and purification, where the availability of cheap and easy-to-make anion receptors would be advantageous.

Acknowledgment. A.D. thanks DST (New Delhi) for financial support.

Supporting Information Available: Synthesis, UV−vis spectra of receptors **1** and **2** with different anions, UV−vis titration curves, color change, discussion on results of electrochemical studies, and Cartesian coordinates of the calculated structures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL048829W

---

(10) Wiberg, K. B.; Rush, D. J. *J. Am. Chem. Soc.* **2001**, *123*, 2038−2046.