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Why, on Interaction of Urea-Based Receptors with Fluoride, Beautiful Colors Develop

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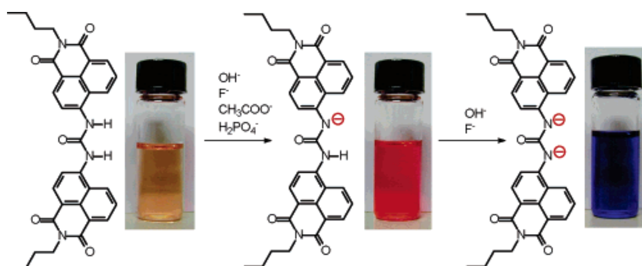
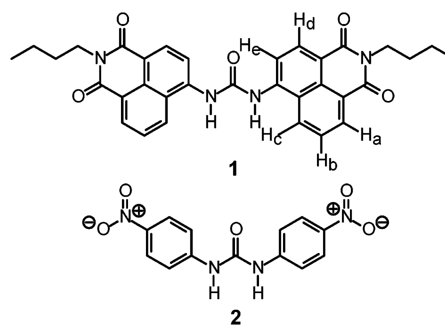


Urea-based receptors, containing electron-withdrawing chromogenic substituents, in a DMSO solution, in the presence of varying excess of fluoride, do not form H-bond complexes, but undergo stepwise deprotonation of the *two* N−H fragments, an event which is signaled by the development of vivid colors. Double deprotonation is also observed in the presence of hydroxide. Less basic anions (CH_3COO^-, $H_2PO_4^-$) induce deprotonation of only one N−H.

There exists a current interest on the synthesis of colorimetric neutral chemosensors for anions.[1] The design usually involves the covalent linking of a chromogenic fragment to a neutral receptor capable of establishing selective interactions with the envisaged anion.[2] In this sense, the receptor must be able to donate to the anion one or more H-bonds, in most cases using the N−H fragment(s) of amides and sulfonamides,[3] pyrroles,[4] ureas.[5] If the N−H group is integrated into the chromogenic subunit, it may happen that the negative charge brought by the anion modifies the dipole associated to the charge-transfer transition (or, in other words, stabilizes the excited state of the chromophore), ultimately leading to a modification of the UV−vis spectrum and to a color change. In this field, the most investigated individual of the vast family of anions is undoubtly fluoride.[6] Such a penchant does not depend on the prominent role played by fluoride ion in biology, medicine, food, and environmental sciences (which is, in any case, respectable),[7] but rather on the fact that fluorine, as the most electronegative atom, rightfully establishes the strongest H-bond interactions, which ensures unbeatable selectivity. Moreover, it must be noticed that, whereas other anions when interacting with a given colorimetric chemosensor induce moderate color changes (e.g., from colorless to pale yellow, from pale yellow to bright yellow), drastic color modifications are often observed with fluoride, to red, to blue, to green. Such a feature has been observed in particular for receptors containing a urea subunit.[8]

In the perspective of elucidating the nature of the color changes developed following fluoride-receptor interaction, we considered system **1**, in which a urea subunit has been equipped with two naphthalenimide moieties. Naphthalenimide is a classical chromophore, whose charge-transfer transition is responsible for the yellow color.



We observed that, on addition of an excess of a few equivalents of $[Bu_4N]F$, the color of a DMSO solution of **1** turned from yellow to red. Then, on further addition of fluoride, up to tens of equivalents, a blue color developed (see the photograph in Figure 1).

Figure 2 shows the family of spectra recorded on titrating a DMSO solution 5.0×10^{-5} M of **1** with a standard DMSO solution of $[Bu_4N]F$. On addition of fluoride, the intensity of the band at 400 nm decreases and a new band develops at 540 nm, the color turning from yellow to red (see spectra in Figure 2a and color change in Figure 1). A red shift of the charge transfer

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(1) Suksai, C.; Tuntulani, T. *Chem. Soc. Rev.* **2003**, *32*, 192−202.
(2) (a) Martinez-Maòez, R.; Sancenón, F. *Chem. Rev.* **2003**, *103*, 4419. (b) Gale, P. A. (Ed.) *Coord. Chem. Rev.* **2003**, *240*, 1−226.
(3) Valiyaveetil, S.; Engbersen, J. F. F.; Verboom, W.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 900−901.
(4) Sessler, J. L.; Cyr, M. J.; Lynch, V.; McGhee, E.; Ibers, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 2810−2813.
(5) (a) Smith, P. J.; Reddington, M. V.; Wilcox, C. S. *Tetrahedron Lett.* **1992**, *41*, 6085−6088. (b) Fan, E.; van Arman, S. A.; Kincaid, S.; Hamilton, A. D. *J. Am. Chem. Soc.* **1993**, *115*, 369−370.
(6) (a) Miyaji, H.; Sato, W.; Sessler, J. L. *Angew. Chem., Int. Ed.* **2000**, *39*, 1777−1780. (b) Mizuno, T.; Wei, W.-H.; Eller, L. R.; Sessler, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 1134−1135. (c) Kubo, Y.; Yamamoto, M.; Ikeda, M.; Takeuchi, M.; Shinkai, S.; Yamaguchi, S.; Tamao, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 2036−2040. (d) Kondo, S.; Nagamine, M.; Yano, Y. *Tetrahedron Lett.* **2003**, *44*, 8801−8804. (e) Solé, S.; Gabbaï, F. P. *Chem. Commun.* **2004**, 1284−1285. (f) Zhou, L.; Zhang, X.; Wu, S. *Chem. Lett.* **2004**, *33*, 850−851. (g) Ghosh, T.; Maiya, B. G.; Wong, M. W. *J. Phys. Chem. A* **2004**, *108,* 11249-11259. (h) Miao, R.; Zheng, Q.-Y.; Chen, C.-F.; Huang, Z.-T. *Tetrahedron Lett.* **2004**, *45*, 4959−4962;
(7) Sohn, H.; Letant, S.; Sailor, M. J.; Trogler, W. C. *J. Am. Chem. Soc.* **2000**, *122*, 5399.
(8) (a) Jose, D. A.; Kumar, D. K.; Ganguly, B.; Das, A. *Org. Lett.* **2004**, *6*, 3445−3448. (b) Lee, J. Y.; Cho, E. J.; Mukamel, S.; Nam, K. C. *J. Org. Chem.* **2004**, *69*, 943−950. (c) Kwon, J. Y.; Jang, Y. J.; Kim, S. K.; Lee, K.-H.; Kim, J. S.; Yoon, J. *J. Org. Chem.* **2004**, *69*, 5155−5157. (d) Vázquez, M.; Fabbrizzi, L.; Taglietti, A.; Pedrido, R. M.; González-Noya, A. M.; Bermejo, M. R. *Angew. Chem., Int Ed.* **2004**, *43*, 1962−1965. (e) Thiagarajan, V.; Ramamurthy, P.; Thirumalai, D.; Ramakrishnan, V. T. *Org. Lett.* **2005**, **7**, 657−660.

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FIGURE 1. Color changes observed on addition of $[Bu_4N]F$ to a DMSO solution of receptor **1** (= LH_2). Left to right: no addition (dominant species: LH_2); plus 5 equiv of $[Bu_4N]F$ (dominant species: LH^-); plus 40 equiv of $[Bu_4N]F$ (dominant species: L^{2-}).

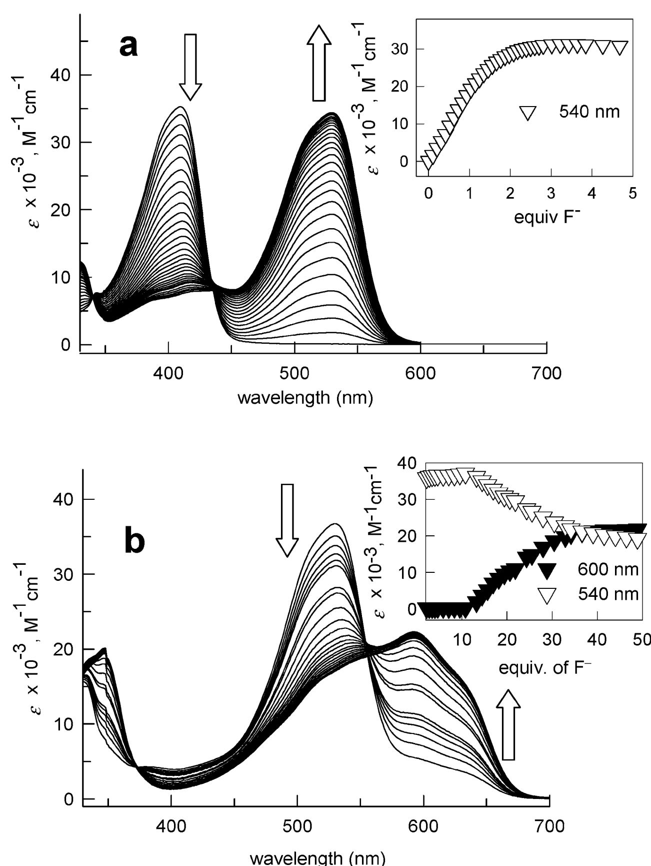
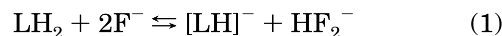


FIGURE 2. Family of spectra taken in the course of the titration of a DMSO solution 5.0×10^{-5} M in receptor **1** (LH_2) with a standard solution of $[Bu_4N]F$, at 25 °C: (a) from 0 to 5 equiv of $[Bu_4N]F$ (the band that develops at 540 nm pertains to the mono-deprotonated receptor $[LH]^-$; (b) from 5 to 50 equiv of $[Bu_4N]F$ (the band that develops at 600 nm pertains to the doubly deprotonated receptor $[L]^{2-}$.

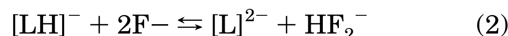
band of a similar substantial extent (from 345 to 475 nm) had been previously observed on interaction of fluoride with the urea based receptor **2**, a feature which had been abscribed to the neat deprotonation of one of the N−H fragments of the urea subunit.[9] Such a circumstance has been corroborated by ^{1}H NMR studies and crystallographic evidence.[9] Thus, it is assumed that, on fluoride addition, receptor **1** (LH_2) undergoes N−H deprotonation. Moreover, the titration profile, shown in the inset of Figure 2a, indicates a 2:1 stoichiometry for the process, which can be therefore described by the following equilibrium:



$$LH_2 + 2F^- \leftrightarrows [LH]^- + HF_2^- \quad (1)$$

The steep curvature of the titration profile prevents from the determination of the constant of equilibrium (1), (log $K > 7$, in the investigated conditions). In any case, the constant of eq 1, K_1, corresponds to the product of the dissociation constant of acid LH_2 (K_{A1}) times the formation constant of HF_2^-, $\beta(HF_2^-)$ (equilibrium: $H^+ + 2F^- \leftrightarrows HF_2^-$): $K_1 = K_{A1} \times \beta(HF_2^-)$. Thus, occurrence of N−H deprotonation must be ascribed to two distinct contributions: (i) the intrinsic acidity of the urea moiety, which has been enhanced by the proximity of two electron-withdrawing substituents, and (ii) the especially high stability of the $[HF_2]^-$ hydrogen-bonding complex.

On addition of a further excess of $[Bu_4N]F$, the color of the solution turns from red to blue (see Figure 1), while in the visible spectrum (see Figure 2b), the band at 540 nm disappears and a new band forms at 600 nm. It is suggested that the new band pertains to the doubly deprotonated receptor $[L]^{2-}$, which forms according to equilibrium (2):

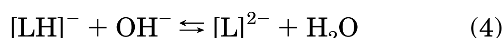


$$[LH]^- + 2F- \leftrightarrows [L]^{2-} + HF_2^- \quad (2)$$

The constant of eq 2, K_2, is related to the second acidity constant of LH_2 and to the formation constant of HF_2^-, according to $K_2 = K_{A2} \times \beta(HF_2^-)$. The titration profile reported in the inset of Figure 2b shows that the band 600 nm, pertinent to the $[L]^{2-}$ species, does not form after 2 equiv addition, but begins to develop after addition of 10 equiv or more of fluoride. This may be due to an especially high value of pK_{a2} of **1** and also to the fact that fluoride is added as a hydrated salt: $[Bu_4N]F{\cdot}3H_2O$. In particular, the presence of a relatively high amount of water may interfere with eq 2 and disfavor the formation of $[L]^{2-}$. In any case, the stepwise deprotonation process is fully reversible, as indicated by the fact that, on progressive addition of water, the blue DMSO solution first turns red, then yellow.

Stepwise deprotonation of **1** is clearly observed on titration with $[Bu_4N]OH$. Spectra in Figure 3a,b show the consecutive development of bands at 540 nm (pertinent to $[LH]^-$) and at 600 nm (pertinent to $[L]^{2-}$). Notice that the titration profile in the inset of Figure 3a indicates 1:1 stoichiometry. Thus, it is hypothesized that the following neutralization equilibria take place:

$$LH_2 + OH^- \leftrightarrows [LH]^- + H_2O \quad (3)$$



$$[LH]^- + OH^- \leftrightarrows [L]^{2-} + H_2O \quad (4)$$

Structural details of $[LH]^-$ and $[L]^{2-}$ species can be obtained from the ^{1}H NMR spectra recorded in the course of the titration of **1** with $[Bu_4N]OH$ in DMSO-d_6, shown

(9) Boiocchi, M.; Del Boca, L.; Esteban-Gómez, D.; Fabbrizzi, L.; Licchelli, M.; Monzani, E. *J. Am. Chem. Soc.* **2004**, *126*, 16507−16514.

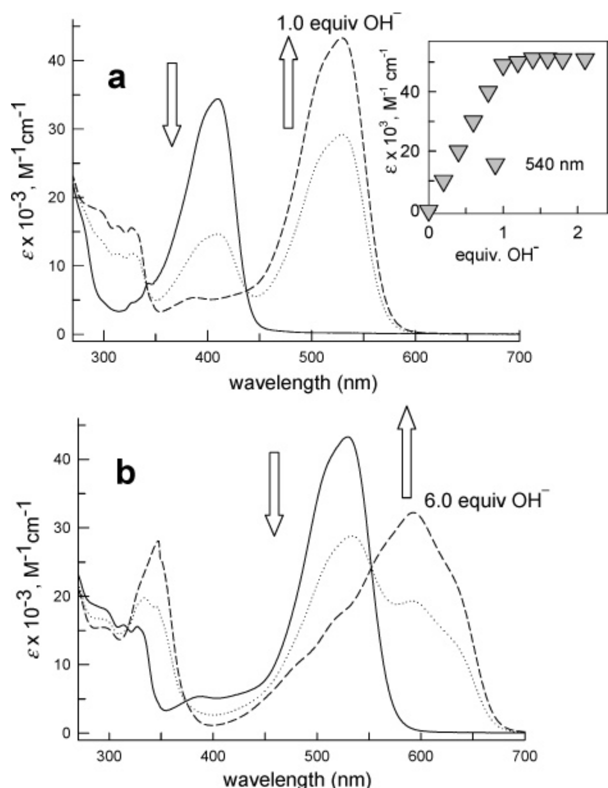


FIGURE 3. Family of spectra taken in the course of the titration of a DMSO solution 5.0×10^{-5} M in receptor **1** (LH_2) with a standard solution of $[Bu_4N]OH$, at 25 °C: (a) from 0 to 1 equiv of $[Bu_4N]OH$ (the band that develops at 540 nm pertains to the mono-deprotonated receptor $[LH]^-$; inset: titration profile on the band at 540 nm; (b) from 1 to 6 equiv of $[Bu_4N]OH$ (the band that develops at 600 nm pertains to the doubly deprotonated receptor $[L]^{2-}$).

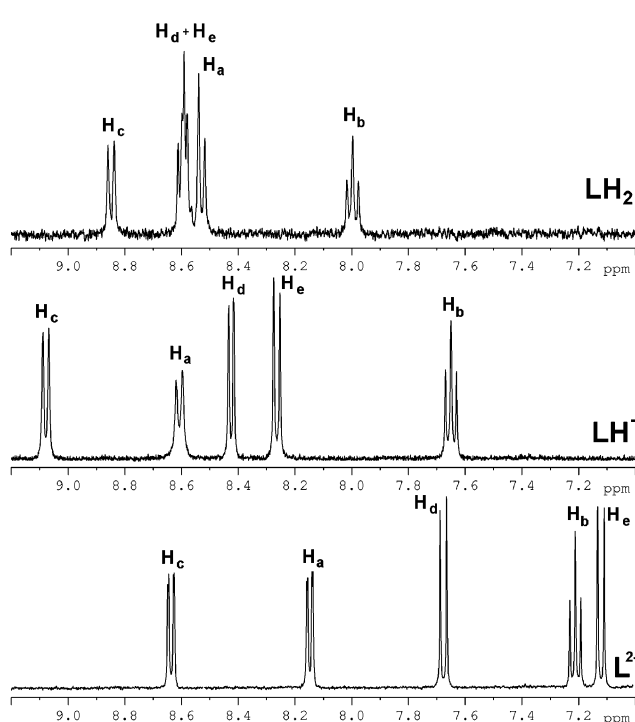


FIGURE 4. ^{1}H NMR spectra taken in the course of the titration of a DMSO-d_6 solution 5.0×10^{-3} m in receptor **1** (LH_2) with a standard solution of $[Bu_4N]OH$. Key: LH_2, no $[Bu_4N]OH$ addition; $[LH]^-$, +1 equiv of $[Bu_4N]OH$; $[L]^{2-}$, +6 equiv of $[Bu_4N]OH$.

in Figure 4. It has been previously shown that urea monodeprotonation is signaled by the significant upfield shift of the protons of the phenyl substituents.[9] Such an effect derives from the through-bond propagation onto the aromatic framework of the electronic charge generated on N−H deprotonation. In the spectra in Figure 4, very large upfield shifts are observed for all C−H protons, on removal of the first and, in particular, of the second proton. Such a through-bond effect is contrasted by a through-space effect, which reflects the electrostatic polarization exerted by the negative charge on the closest C−H protons. This latter effect should induce a downfield shift. Indeed, downfield shift is observed, following the first deprotonation, on the H_c proton, which is the closest to negatively charged nitrogen atom. On second deprotonation, the through-bond effect is so strong that the polarization effect is totally surmounted and also the H_c proton undergoes a drastic upfiled shift. A similar pattern was observed on titration with fluoride.

It has to be noted that second deprotonation of **1** is induced by hydroxide and fluoride and not by other anions. Acetate induces deprotonation of one N−H fragments, according to a 1:1 stoichiometry (which defines the following acid−base equilibrium: $LH_2 + CH_3COO^- \leftrightharpoons [LH]^- + CH_3COOH$, with a log $K = 4.97 \pm 0.01$), but no appearance of the band at 600 nm and development of the blue color are observed, even after the addition of a huge excess of the tetrabutylammonium salt. The less basic anion $H_2PO_4^-$ removes one proton from **1**, but only after large excess addition. No deprotonation is observed with less basic oxoanions such as NO_2^-, NO_3^-, HSO_4^-, and the remaining halides Cl^- and Br^-. Thus, interaction selectivity of the urea-based system **1**, signaled by the development of vivid colors, is solely related to the pK_a of the anion and to consequent capability of abstracting an H^+ from the receptor: $OH^- > CH_3COO^- > H_2PO_4^-$. Fluoride is a special case: F^- itself is not an especially strong base (p$K_a = 15 \pm 2$, in DMSO);[10] however, *two* F^- ions behave as a very strong base and exhibit a large affinity toward H^+, which is second only to OH^- (pK_a = 32, in DMSO)[10] and is due to the unique stability of the H-bond complex $[HF_2]^-$.[11]

Fluoride- and hydroxide-induced double deprotonation should be observed in any urea-based receptors, made acidic enough by the presence of electron-withdrawing substituents. As an example, receptor **2** undergoes a similar two-step deprotonation, with pale-yellow-to-orange and orange-to-violet color changes. Parts a and b of Figure 5 show the family of spectra observed during the titration of a DMSO solution of **2** with $[Bu_4N]OH$: the band at 485 nm pertains to $[LH]^-$ and the band at 540 nm to $[L]^{2-}$. The two bands develop according to equilibria (3) and (4). On the other hand, the addition of a large excess of CH_3COO^- and $H_2PO_4^{2-}$ induced only the first deprotonation.

It must be mentioned that solvent plays its own role. In fact, in the less polar MeCN, receptor **2**, on $[Bu_4N]F$

(10) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456−463.
(11) Gronert, S. *J. Am. Chem. Soc.* **1993**, *115*, 10258−10266.

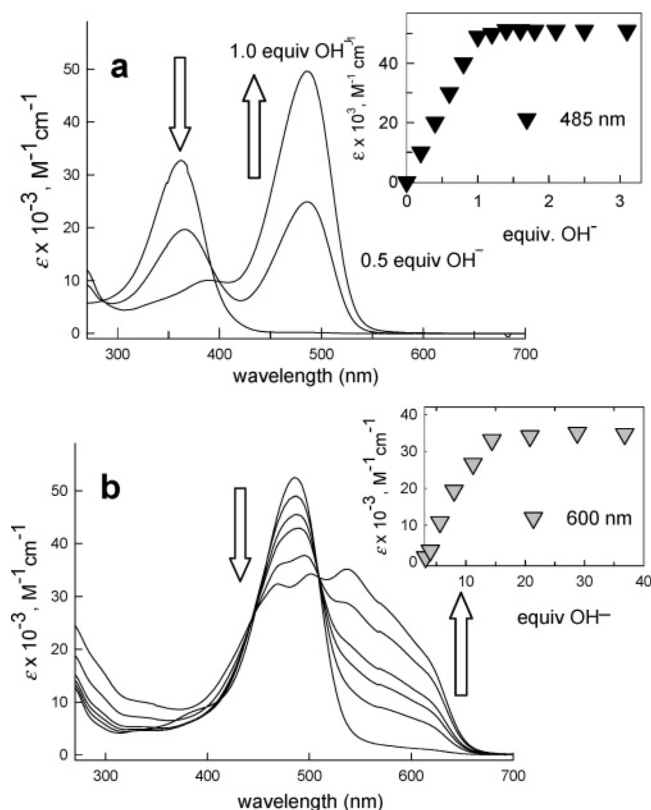
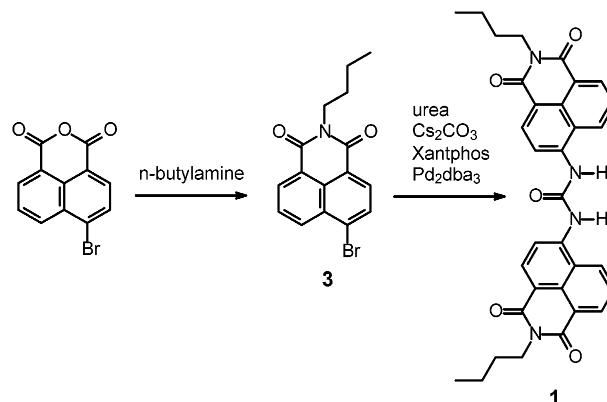


FIGURE 5. Family of spectra taken in the course of the titration of a DMSO solution 5.0×10^{-5} m in receptor **2** (LH_2) with a standard solution of $[Bu_4N]OH$, at 25 °C: (a) from 0 to 1 equiv of $[Bu_4N]OH$ (the band that develops at 485 nm pertains to the mono-deprotonated receptor $[LH]^-$; (b) from 1 to 40 equiv of $[Bu_4N]OH$ (the band that develops at 540 nm pertains to the doubly deprotonated receptor $[L]^{2-}$.

addition, first gives an authentic H-bond complex, $[LH_2\cdots F]^-$, and then, at the second equivalent of titrant, undergoes deprotonation to give $[LH]^-$.[9] However, even a huge addition of $[Bu_4N]F$ does not induce any further color change and modification of the UV−vis spectrum. Thus, it appears that deprotonated forms are stabilized by solute−solvent interactions, and in particular, only the highly polar DMSO favors the formation of $[L]^{2-}$ anions of **1** and **2**. Notice that in MeCN solution acetate does not induce deprotonation of the first N−H fragment but forms with **2** a genuine H-bond complex, $[LH_2\cdots CH_3COO]^-$.[9] Receptor **1** could not be investigated in MeCN (and solvent effect could not be evaluated) due to its very low solubility.

This study has shown that the very high affinity of fluoride toward N−H containing molecules, in particular urea derivatives, rather than to the ability of F^- to establish especially strong hydrogen bonding interactions with the receptor, may be due to the very high stability of the HF_2^- complex, whose formation allows N−H deprotonation. Appearance of intense and beautiful colors, which may vary depending upon analyte concentration, is not an indication of the strength of the H-bond, but reflects the intensity of the dipole responsible for the charge-transfer transition within the deprotonated species, $[LH]^-$ and $[L]^{2-}$. The above considerations should not prevent from the colorimetric determination of the fluoride ion in fluids by urea derivatives, which is indeed very efficient and suffers from the interference of only one analyte, hydroxide. Operators are advised that the recognition process under investigation does not take place within the sophisticated realm of supramolecular chemistry, but rightfully belongs to the old and congested class of Brønsted acid−base reactions.

SCHEME 1. Synthetic Route to 1



Experimental Section

General Procedures and Materials. All reagents for syntheses were purchased by Aldrich/Fluka and used without further purification. UV−vis spectra were recorded on a Varian CARY 100 spectrophotometer, with a quartz cuvette (path length: 1 cm). The cell holder was thermostated at 25.0 °C, through circulating water. ^{1}H NMR spectra were obtained on a Bruker AVANCE400 spectrometer (400 MHz), operating at 9.37 T.

N,N′-(Bis-*N*-butyl-1,8-naphthalenimide)urea (1) (Scheme 1). To a solution of 4-bromo-*N*-butyl-1,8-naphthalenimide, 3,[12] (0.200 g, 0.603 mmol) in 4 mL of dioxane were added urea (0.0235 g, 0.392 mmol), Cs_2CO_3 (0.275 g, 0.844 mmol), Pd_2dba_3−$CHCl_3$ (0.003 g, 0.5 mol %), and Xantphos (0.0156 g, 3 mol %). The reactor was degassed by evacuation and filled with argon. The mixture was heated at 100 °C under magnetic stirring, while the progress of the reaction was monitored through TLC (hexane/ethyl acetate, 7:3). On completion of the reaction (12 h), the mixture was cooled to room temperature and the content of the reactor was poured into 50 mL of a saturated KCl aqueous solution. The solution was extracted with ethyl acetate (4 × 5 mL), and the combined extracts were washed with an aqueous KCl solution. From the organic phase, a solid product formed that was separated by filtration to give an air stable yellow solid (0.140 g., 83%), soluble in DMSO and insoluble in all other common solvents. ^{1}H NMR (DMSO-d_6, δH ppm, TMS): aromatic region δ 8.85 (d, $J_{c,b}$ = 8.6 Hz, 2H; Hc), 8.60 (m, 4H; Ha and He), 8.53 (d, $J_{d,e}$ = 8.6 Hz, 2H; Hd), 8.00 (false t, J_{obs} = 8.0 Hz, 2H; Hb); IR spectrum (Nujol mull, cm^{-1}) 3292 (NH); 1699, 1656 (C=O); 1553 (CN); ESI-mass: *m/z* (negative ion mode) 561.1 (M − H$^+$, 100), 597,1 (M + Cl$^-$, 38). Anal. Calcd for $C_{33}H_{30}N_4O_5$: C, 70.45; H, 5.37; N, 9.96. Found: C, 70.52; H, 5.39; N, 9.96.

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(12) Gan, J.; Tian, H.; Wang, Z.; Chen, K.; Hill, J.; Lane, P. A.; Rahn, Fox, A. M.; Bradley, D. D. C. *J. Organomet. Chem.* **2002**, *645*, 168−175.