Tetrahedron Letters 52 (2011) 1503-1505

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

3-Urea-1,8-naphthalimides are good chemosensors: a highly selective dual colorimetric and fluorescent ICT based anion sensor for fluoride

Rebecca M. Duke, Thorfinnur Gunnlaugsson*

School of Chemistry, Centre for Synthesis and Chemical Biology, Trinity College Dublin, Dublin 2, Ireland

ARTICLE INFO

Article history: Received 18 October 2010 Revised 19 January 2011 Accepted 25 January 2011 Available online 1 February 2011

ABSTRACT

The 1,8-naphthalimide sensor 1 was developed as a colorimetric and fluorescent sensor for anions. Being the first example of such anion sensors, where the 3-position of the naphthalimide ring is used to incorporate the anion recognition moiety, in this case a trifluromethyl derived aryl urea moiety, the sensors gave rise to significant changes in both the absorption and the emission spectra, which were both red shifted upon interacting with anions. The changes were most pronounced for fluoride, and to a lesser extent for acetate and hydrogen phosphate, in DMSO, making 1 a highly selective sensor for F^- .

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The development of colorimetric and fluorescent sensing of anions has become a highly active area of research within the field of supramolecular chemistry.^{1–5} Sensors based on the 4-amino-1,8naphthalimide structure have been used extensively in anion sensing design,^{2,6–10} where various types of anion receptor moieties have been attached or conjugated to the naphthalimide moiety, either at the 4-amino site or via the imide moiety.^{2,11} We have recently demonstrated that hydrogen bonding urea or thiourea receptors can, when conjugated at the 4-position via a hydrazide spacer, function as effective colorimetric sensors for anions such as acetate (AcO⁻) and hydrogen phosphate (HPO₄⁻) as well as fluoride (F⁻) and chloride (Cl⁻) in either organic (DMSO or CH₃CN) or aqueous solutions.^{11,12} Concurrently, Fabbrizzi et al. developed urea-based di-naphthalimide sensors, where a single urea moiety bridged two naphthalimide units at their 4-positions.¹³

In this Letter, we present, to the best of our knowledge, the first example of an anion sensor based on derivatising the 3-position of the naphthalimide moiety with an anion receptor. Our system, 1, is based on the use of a simple urea moiety connected to the 3-position of the naphthalimide, starting from compound 2 (Scheme 1). As with 4-amino-naphthalimide based sensors, this new system also takes advantage of the internal charge transfer (ICT) character of the fluorophore, where the urea acts as an electron donor (via the NH-moiety), and the imide as an electron acceptor. We foresaw that this design would recognise anions through hydrogen bonding, which would give rise to concomitant changes in the photophysical properties of the 1,8-naphthalimide, and thereby would demonstrate the versatility of this building block in such anion sensing. Only a few examples of 3-naphthalimide-based sensors have been developed to date,¹⁴ and to the best of our knowledge, none have been developed for anion sensing, while a few have



Scheme 1. Synthesis of anion sensor 1.

been synthesised as potential anticancer agents.¹⁵ Hence, there exists an unexplored opportunity to investigate the use of this fluorophore in anion sensing.

The synthesis of sensor 1, was achieved in three steps from commercially available 3-nitro-1,8-naphthalic anhydride, which was reduced to the corresponding 3-amino-1,8-naphthalic anhydride at room temperature using 10% Pd/C at 3 atm in DMF. Subsequent reaction, under reflux, with ethylamine in 1,4-dioxane for 16 h, giving the desired imide **2**,¹⁶ as an orange solid, in 51% yield after aqueous work-up. This product was then reacted with 1 equiv of 4-trifluoromethylphenyl isocyanate in MeCN for 16 h under reflux. This resulted in precipitation of the desired urea which was collected and dried in air, giving product **1**¹⁷ as an off-white solid in 83% yield (Scheme 1). The product was characterised using analytical techniques. For example, the ¹H NMR (400 MHz, DMSO- d_6) spectrum of 1 showed two broad singlets at 9.41 and 9.22 ppm characteristic of urea protons (Fig. 1), while the ¹³C NMR (100 MHz, DMSO- d_6) spectrum showed the expected number of resonances.

The absorption spectrum of **1** was recorded in DMSO. Unlike that seen for the previously described 4-amino-1,8-naphthalimide-based anion sensors,² the ICT transition of **1** was not as pronounced, being shifted to shorter wavelengths, with a λ_{max} at 394 nm and a second band at 340 nm. This is to be expected as



^{*} Corresponding author. Tel.: +353 1 896 3459; fax: +353 1 671 2826. *E-mail address:* gunnlaut@tcd.ie (T. Gunnlaugsson).

^{0040-4039/\$ -} see front matter @ 2011 Elsevier Ltd. All rights reserved. doi:10.1016/j.tetlet.2011.01.099



Figure 1. The ¹H NMR spectrum of sensor 1 (400 MHz, DMSO-d₆).

the push–pull character of this isomer is not as strong as that seen, for instance, in Farbbrizzi's anion sensor¹³ discussed above, and that of our own work and others,^{6,11} where the ICT band is normally red shifted by ca. 40–50 nm. This clearly demonstrates the difference in the electronic donor ability of the 3- versus the 4-amino moiety in such structures. Excitation at these wavelengths, gave rise however, on both occasions, to a broad emission centred at 453 nm, tailing into the 600 nm region.

The anion binding abilities of **1** were next investigated using absorption and fluorescence emission spectroscopy. Interestingly, only minor changes occurred in the absorption and the fluorescence emission spectra of **1** upon titration with the TBA salts of $H^2PO_4^-$ or AcO^- (Fig. 2A and B). We were however able to analyse these small changes by plotting the changes as a function of added anion, and while we were unable to determine the binding constant for these changes, the analysis demonstrated a 1:1 binding between the sensor and the anions, which would be expected to occur through hydrogen bonding at the urea moiety.



Figure 2. (A) The changes in the absorption spectra of **1** $[1.2 \times 10^{-5} \text{ M}]$ upon addition of AcO⁻ (0–25 equiv) in DMSO. (B) The corresponding changes in the florescence emission spectra, demonstrating that the sensor does not respond effectively to the anion.

Similar to that observed above, titration of **1** with F^- (as a TBAF·3H₂O salt) gave a minor increase in the absorption spectrum at short wavelengths (ca. 329 nm), indicating interaction of F^- at the phenyl based receptor, Figure 3. These changes also occurred with a small bathochromic shift in the naphthalimide ICT transition, centred around 390 nm. However, in contrast to these changes, after the addition of ca. 25 equiv of F^- , significantly larger changes were observed in the absorption spectra at both of these wavelengths. Figure 4, demonstrates the overall changes observed (0–100 equiv of F^-), where the ICT band decreased in absorbance,



Figure 3. The changes in the absorption spectra of **1** $[1.2 \times 10^{-5} \text{ M}]$ upon addition of F⁻ (0–25 equiv) in DMSO, demonstrating a small red shift in the ICT transition upon binding of the anion at low concentration.



Figure 4. The changes in the absorption spectra of $\mathbf{1}$ [1.2×10^{-5} M] upon addition of F⁻ (0–100 equiv) in DMSO, demonstrating that the anion can interact with the urea moiety, giving rise to large changes in the ground state properties of the sensor.

with concomitant formation of a long wavelength absorption band, centred at ca. 495 nm, and with the formation of a 'pseudo' isosbestic point (e.g., a small shift being observed for this isosbestic point at higher equivalents of F⁻) at 426 nm. Large changes were also observed at shorter wavelengths, where the absorption band at 327 nm was enhanced dramatically, but these changes were also accompanied with a large decrease in the absorbance band centred at 272 nm, and previously assigned to the phenyl part of the urea receptor moiety. As for the long wavelength changes, two 'pseudo' isosbestic points were observed at 370 and 397 nm, respectively. These changes were similar to those seen upon interactions of fluoride with anion receptor derivatives via the 4-amino moiety of the naphthalimide structure,⁶ indicating a potential common mechanism, that is, deprotonation of the urea proton adjacent to the naphthalimide occurred at high concentrations of F⁻. Additionally, these changes were reversed upon the addition of protic solvents such as MeOH or H₂O. The above changes in the absorption spectra were also clearly visible to the naked eye, where the colour changed from light yellow to red, enabling the use of **1** as a colorimetric sensor for F⁻.

In contrast to the minor changes in the absorption spectrum at low concentration of F^- , large changes were seen in the fluorescence emission spectrum of the ICT transition within the same concentration range. Here, the naphthalimide emission was quenched by ca. 75% in the presence of ca. 50 equiv of F^- , as shown in Figure 5. Concomitantly, smaller enhancements were also seen at lower wavelengths (e.g., ca. 410 nm as shown in Fig. 5) and at long wavelength, ca. 650 nm, but analysis of the long wavelength changes did not give accurate binding information. The changes in the fluorescence emission intensity as a function of anion equivalents for the changes in the ICT band are shown in the insert to Figure 5, and the results indicate that a two-step process occurred over the course of the titrations, which was most likely due to hydrogen bonding to the urea receptor followed by deprotonation at higher concentrations of the anion.

In summary, we have developed 3-urea-1,8-naphthalimide **1** as a fluorescent sensor for anions. We have demonstrated that the anion sensing is most likely to occur via deprotonation of the urea receptor at high concentration making this a highly selective sensor for basic anions such as fluoride. This feature has both environmental and biological relevance, at the same time as demonstrating that the 3-amino moiety of the 1,8-naphthalimide can be employed in anion sensing. We are currently working on developing novel sensors where the 3- and 4-positions of this versatile fluorophore are derivatised with a view to improving both the sensitivity and the selectivity of the anion recognition through synergetic action of more than one hydrogen bonding donor.

800 800 600 700 400 nten 600 200 500 Intensity 400 10 20 30 40 50 60 70 80 90 100 0 Guest Equivalents 300 200 100 0 400 450 500 550 600 Wavelength (nm)

Figure 5. The changes in the fluorescence emission spectra of 1 $[1.2 \times 10^{-5} \text{ M}]$ upon addition of F⁻ (0–100 equiv) in DMSO. Insert: The changes at 455 nm as a function of equivalents of guest added.

Acknowledgements

We like to thank TCD (College award to R.M.D.), Science Foundation Ireland for grant SFI RFP 2008, and HEA-PRTLI Cycle 3 and Cycle 4 (CSCB) for financial support. We thank Dr. John E. O'Brien for assisting with NMR measurements and Dr. Emma B. Veale for helpful discussions.

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- 2-*Ethyl-5-aminobenzo[d,e]isoquinoline-1,3-dione* (2). 3-Amino-1,8-naphthalic anhydride (0.25 g, 1.18 mmol) and 70% ethylamine were refluxed in 1,4-dioxane for 16 h. The reaction mixture was poured into H₂O and the resulting precipitate was isolated by suction filtration to give 2 as an orange solid (0.14 g, 51%). Mp 275–277 °C (Lit. mp¹⁸ 276 °C); δ_H (400 MHz, DMSO-*d*₆), 8.07 (1H, d, *J* = 7.0 Hz, Naph-H₇), 8.02 (1H, d, *J* = 7.6, Naph-H₅), 7.96 (1H, s, Naph-H₂), 7.60 (1H, dd, *J* = 8.16 and 7.60 Hz, Naph-H₆), 7.27 (1H, s, Naph-H₄), 6.00 (2H, br s, NH₂), 4.04 (2H, q, *J* = 7.0 Hz, NCH₂), 1.18 (3H, t, *J* = 7.0 Hz, CH₃); δ_c (100 MHz, DMSO-*d*₆), 163.8 (C=O), 163.7 (C=O), 148.1 (q), 133.8 (q), 131.7 (CH), 127.3 (CH), 122.6 (CH), 122.9 (q), 122.1 (CH), 121.9 (q), 120.8 (q), 112.0 (CH), 34.9 (CH₂), 13.4 (CH₃).
- 17. 2-Ethyl-5-[(4-trifluoromethylphenyl)ureidocarbamoyl]-benzo[d,e]isoquinoline-1,3dione (1). Compound 2 (0.380 g, 1.58 mmol) and 4-trifluoromethylphenyl isocyanate (0.296 g, 1.58 mmol) were refluxed in MeCN for 24 h. The resulting precipitate was isolated by suction filtration to give a beige solid (0.515 g, 76%). Mp 337-339 °C; Anal. Cacld for C₂₂H₁₆N₃O₃F₃: C, 61.83; H, 3.77; N, 9.83. Found: C, 61.65; H, 3.81; N, 9.65. HRMS (ES*): Calcd for C₂₂H₁₇N₃O₃F₃ [M+H]*: 428.1222. Found: 428.1242; δ_H (400 MHz, DMSO-d₆), 9.41 (1H, s, NH_{urea}), 9.22 (1H, s, NH_{urea}), 8.48 (2H, d, *J* = 8.2 Hz, Naph-H_{7,5}), 8.27 (2H, d, *J* = 7.5 Hz, Naph-H_{2,4}), 7.77-7.70 (3H, m, Naph-H₆, Ar-H), 7.64 (2H, d, *J* = 7.9 Hz, Ar-H), 4.05 (2H, d, *J* = 6.7 Hz, NCH₂), 1.22 (3H, t, *J* = 6.7 Hz, CH₃); δ_c (100 MHz, DMSO-d₆) 163.4 (C=O), 163.2 (C=O), 152.6 (q), 143.4 (q), 138.5 (q), 133.6 (CH), 132.4 (q), 128.7 (CH), 127.7 (CH), 126.3 (CH), 124.9 (q, *J*³C-¹⁹F = 27O=Hz), 123.7 (q), 123.6 (CH), 122.8 (q), 122.4 (CF₃, *J*³C-¹³F = 32 Hz), 122.1 (q), 120.1 (CH), 119.8 (CH), 35.0 (CH₂), 13.4 (CH₃); δ_N (60 MHz, DMSO-d₆), 111.0, 111.6; IR (solid) v_{max} (cm⁻¹) 3371, 3304, 1656, 1555, 1326, 1231, 1154, 1110, 1068, 1055, 1017, 843, 787, 686.
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