Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 6271

www.rsc.org/obc

COMMUNICATION

A new *N*-imidazolyl-1,8-naphthalimide based fluorescence sensor for fluoride detection†

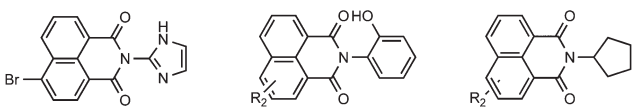
Junqi Wang, Lingyun Yang, Chen Hou and Haishi Cao*

Received 11th May 2012, Accepted 27th June 2012
DOI: 10.1039/c2ob25903f

A chemosensor is reported with high sensitivity and selectivity for detection of fluoride anion. The recognition mechanism is attributed to a fluoride-triggered disruption of the hydrogen bond between imidazole and naphthalimide moieties, resulting in a noncoplanar geometry with low fluorescence.

Fluoride (F^-) is an essential anion in nature and plays important roles in food processing, clinical analysis and fluorination of water supplies, which means that a robust and quantitative method for the analysis of fluoride is essential.[1] Among current analytical approaches, fluorescence sensing is a nondestructive and sensitive means that translates molecular recognition into a tangible fluorescence signal.[2] Numerous approaches have been suggested to develop fluorescence sensors on the basis of various signaling mechanisms for fluoride detection.[3] However, current sensors still lack the sensitivity and selectivity for the robust detection of fluoride.[4]

As a fluorophore, *N*-aryl-1,8-naphthalimide has been widely used for fluorescence sensing due to its high photostability, large Stokes shift, and dual fluorescence properties.[5] Moreover, well characterized spectroscopic and photophysical features of naphthalimide facilitate development of fluorescence sensors on the basis of various sensing mechanisms, which include photo-induced electron transfer (PET), internal charge transfer (ICT) and fluorescence resonance energy transfer (FRET).[6] For example, the strong substituent effect of position 3 and 4 on the naphthalene ring as well as the geometry, size and electronic effect of substituents significantly influence the spectral properties of *N*-aryl-1,8-naphthalimides.[7] Currently, this feature has been extensively used to design signal switches for 1,8-naphthalimide-based fluorescence sensors.[8] However, the contribution of the other important part of *N*-aryl-1,8-naphthalimides, *i.e.*, the aryl moiety, on the photophysical properties of *N*-aryl-1,8-naphthalimides is not well understood, and may facilitate the development of fluorescence sensors.[9]



Scheme 1 Structures of the fluoride chemosensor (**1c**) and control compounds.

Herein, we report the design and synthesis of a new chemosensor based on *N*-imidazolyl-1,8-naphthalimide with high sensitivity and specificity for fluoride detection that involves changes in the structural interaction between the naphthalimide and aryl moieties (Scheme 1). Of nine compounds surveyed, **1c** displays a strong fluorescence emission at 442 nm, indicative of a rigid structure formed by a intramolecular hydrogen bond (H-bond) between imidazole H and carbonyl O atoms. In the presence of fluoride, the disruption of this H-bond leads to significant fluorescence quenching, which provides a sensitive means of fluoride detection.

The synthetic route to nine fluorogenic molecules **1a–3c** is summarized in Scheme 2. In consideration of how to best construct a system with strong H-bonding between aryl and naphthalimide moieties, 2-aminoimidazole, 2-aminophenol and cyclopentylamine were used to prepare the R_1 moieties. Also, three different substituents on the naphthalene ring (R_2 = Br, NH_2, and H) were selected to illustrate the substituent effect on the photophysical properties of 1,8-naphthalimides. The compounds (**1a–1c** and **3a–3c)** were readily prepared in one step by the condensation of the anhydride with the amine. Compounds **2a–2c** were synthesized in two steps. Refluxing of 3-nitro-1,8-naphthalic anhydride with $SnCl_2$ in 15% HCl for 2 h afforded the 3-amino-1,8-naphthalic anhydride,[10] which was then reacted with three primary amines (2-aminoimidazole, 2-aminophenol and cyclopentylamine) to give **2a–2c**. The structures of **1a–3c** were confirmed by ^1H NMR, ^{13}C NMR, and elemental analysis (see ESI†).

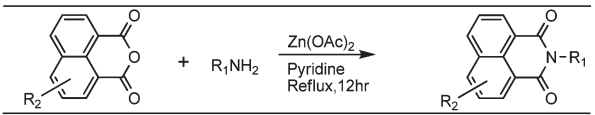
Photospectroscopic properties of **1a–3c** were characterized by UV-vis absorption and fluorescence emission spectra at 25 °C in CH_2Cl_2 (Table 1). **1a** and **1b** containing cyclopentyl and phenyl groups as R_1 respectively exhibited maximum absorption bands

University of Nebraska at Kearney, Department of Chemistry, Kearney Nebraska, 68849, USA. E-mail: caoh1@unk.edu; Fax: +1-3088658399; Tel: +1-3088658105

† Electronic supplementary information (ESI) available: Detailed synthetic procedures and characterization data for **1a–3c**; ^1H and ^{13}C NMR spectra; calculation of binding constant for **1c**; F^- titration for **1a–3a** and **1b–3b** in CH_2Cl_2. See DOI: 10.1039/c2ob25903f

at 343 nm and fluorescence emission bands at 391 nm. **1c** with an imidazolyl group as R_1 displayed a major absorption peak at 328 nm with a shoulder peak at 413 nm, and an emission peak at 442 nm. Compounds **2a–2c** showed an absorption maximum in the range of 342–344 nm and an emission maximum between 471–479 nm; variation in spectral properties was due to the amino substitution on naphthalene ring. Compounds **3a–3c** displayed an absorption maximum between 330 to 335 nm and an emission maximum between 375 to 385 nm. In contrast to **1a** and **1b**, **1c** showed peaks with longer wavelength in both absorption and emission spectra that suggested a significant contribution of imidazole group (R_1) to the spectral properties of **1c**.

To explain the photospectroscopic behavior of **1c**, quantum chemical calculations were carried out at the Hartree–Fock/6-31G* level for all of nine compounds (Table 2).[11] The distance (1.807 Å) of C═O···H–R_1 in **1c** strongly supported the presence of an intramolecular H-bond between the O atom in the carbonyl group and the H atom in the imidazole. Also, the dihedral angle between the aryl/cycloalkyl ring and the naphthalimide ring was calculated because the conformation and geometry of these two moieties can significantly affect the fluorescence properties of 1,8-naphthalimides.[12] The dihedral angle (0.30°) determined for **1c** also bolstered a coplanar geometry of **1c**. Moreover, the calculated dihedral angles of **2c** and **3c** were found to also be small (1.40°) indicating that these two molecules possess a near coplanar geometry. Considering the distance of C═O···H–R_1 (1.813 Å) in **2c** and **3c**, these two molecules also might form intramolecular H-bonds. For the remaining six molecules, their calculated dihedral angles varied between 47.9° and 56.4° with longer distances of C═O···H–R_1 (1.985–1.987 Å) that implied a nonplanar geometry between the aryl/cycloalkyl ring and the naphthalimide ring.



Entry	R_1	R_2	Yield (%)
1a		Br	78
1b		Br	54
1c		Br	27
2a		NH_2	63
2b		NH_2	56
2c		NH_2	31
3a		H	81
3b		H	83
3c		H	42

Scheme 2 Compounds **1a–3c** were readily prepared by the condensation of anhydride with amine.

According to the quantum chemical calculations, **1c**, **2c**, and **3c** showed the potential ability to form an intramolecular hydrogen bond that resulted in a coplanar geometry between naphthalimide and imidazole moieties. Our hypothesis is that, in the presence of F^-, the intramolecular H-bond will be disrupted due to the strong interaction between F^- and H atom in the imidazole moiety and consequently will cause a spectroscopic change. Based on this hypothesis, **1c**, **2c**, and **3c** were chosen to investigate the concentration-dependent changes in the absorption spectra upon addition of F^- (TBAF) in dichloromethane (Fig. 1). All three molecules (1.0×10^{-3} M) displayed a major absorption in the 330–340 nm region. With the addition of F^- (1 equiv), no significant change in absorption was observed for **2c** and **3c**, but a significant decrease of the absorption peak centered at 413 nm was observed for **1c**. The absorption change for **1c** indicated the disruption of a H-bond between imidazole and naphthalimide moieties in the presence of F^- that was consistent with previous calculation. Fluorescence titrations were conducted upon incubation of **1c**, **2c** and **3c** (5.0×10^{-6} M) with F^- (0–10 equiv) for 1 min at room temperature. As displayed in Fig. 2a, **1c** displayed a significant decrease in the fluorescence emission at 442 nm, with maximum quenching (94%) upon addition of 1 equiv F^-. In contrast, although **2c** and **3c** also showed the fluorescence decreasing, only 29% and 33% quenching were observed respectively in the presence of 10 equiv F^- (Fig. 2b and 2c). These titration results obviously indicated that F^- can effectively disrupt the intramolecular H-bond in **1c** reflected by fluorescence quenching. Moreover, the F^- titrations also were carried out for

Table 1 Photospectroscopic properties of **1a–3c** in CH_2Cl_2

	1a	**1b**	**1c**	**2a**	**2b**	**2c**	**3a**	**3b**	**3c**
λ_{ab} (nm)	343	343	328	342	342	344	330	335	330
λ_{em} (nm)	391	391	442	471	479	476	385	383	375
Φ_f (10^{-3})	0.7	0.7	18	89	5.2	33	0.9	0.5	12

Table 2 Calculated dihedral angles between the aryl ring and the naphthalimide ring and H-bond length of C═O···H–R_1

	1a	**1b**	**1c**	**2a**	**2b**	**2c**	**3a**	**3b**	**3c**
Dihedral angle (°)	56.4	48.1	0.30	56.2	48.8	1.40	52.4	47.9	1.40
H-bond length (Å)	—	1.985	1.807	—	1.986	1.813	—	1.987	1.813

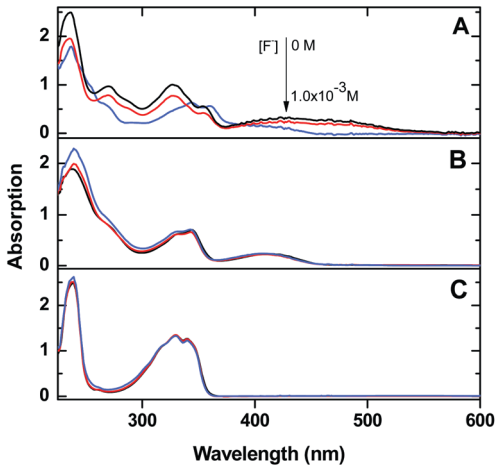


Fig. 1 Absorption spectra of **1c** (A), **2c** (B), and **3c** (C) (1.0×10^{-3} M) acquired in dichloromethane upon addition of F^- (black line: 0 M, red line: 0.5×10^{-3} M, blue line: 1.0×10^{-3} M).

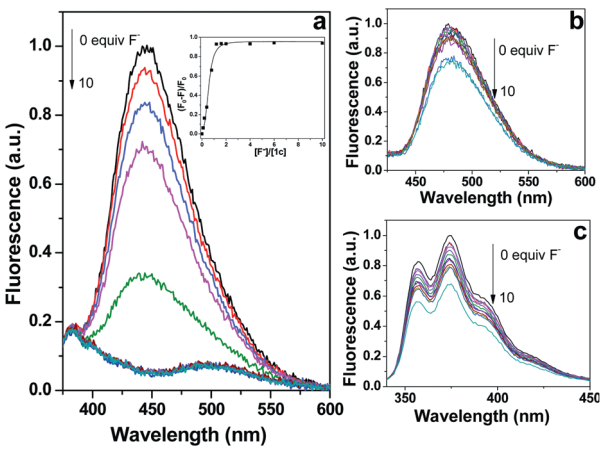
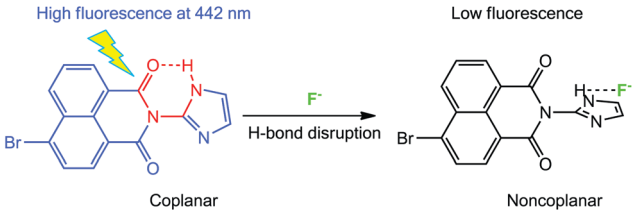


Fig. 2 Decreases in fluorescence emission spectra in the presence of increasing amounts of F^- (TBAF) (incrementally increased between 0–10 equiv) for 5.0×10^{-6} M of (a) **1c** (λ_{ex} = 344 nm), (b) **2c** (λ_{ex} = 344 nm), and (c) **3c** (λ_{ex} = 330 nm) in CH_2Cl_2 at room temperature.

1a–3a and **1b–3b**, but no fluorescence quenching was observed (Fig. S1†).

Fig. 2a shows that **1c** exhibited a remarkably high sensitivity to F^- such that 5.0×10^{-7} M F^- caused 6% fluorescence quenching and the maximum quenching was achieved in the presence of 5.0×10^{-6} M F^-. The titration shown in Fig. 2a suggested that **1c** formed a complex with F^- as indicated by the decrease of fluorescence at 442 nm. The stoichiometry and association constant of **1c**–F^- were investigated by using the program SPECFIT. The fluorescence titration of **1c** were best fitted to 1 : 1 stoichiometry with an association constant of log $K_a = 5.31 \pm 0.07$ by nonlinear regression analysis.[13]

On the basis of the spectral change of **1c** upon addition of F^-, the fluorescence emission at 442 nm can be reasonably attributed to the coplanar geometry formed by intramolecular H-bond between naphthalimide and imidazole moieties. As noted above, in the absence of F^-, **1c** possessed a rigidly coplanar geometry



Scheme 3 Proposed mechanism of fluorescence quenching for **1c** upon addition of fluoride involved a disrupting intramolecular H-bond.

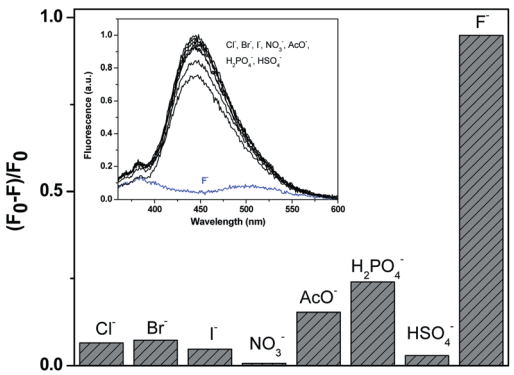


Fig. 3 Anion selectivity of **1c** (5.0×10^{-6} M) in CH_2Cl_2 upon addition of 1 equiv of the indicated anions (λ_{ex} = 344 nm, λ_{em} = 442 nm).

that displayed a strong fluorescence emission at 442 nm. However, when F^- was added, the original intramolecular H-bond was disrupted due to the stronger interaction between F^- and NH group on imidazole moiety. As the result, the whole molecule lost coplanar structure as revealed by significant fluorescence quenching (Scheme 3). For comparison, the F^- titrations also have been carried out under the same conditions for molecules without intramolecular H-bond in between (**1a**, **2a** and **3a**) and molecules containing H-bond but without coplanar structure (**1b**, **2b** and **3b**), none of them showed any fluorescence change upon addition of F^-. These results further confirmed that the coplanar structure formed by intramolecular H-bond played a central role for the spectral properties of **1c**. In presence of F^-, many fluoride chemosensors have been reported for the deprotonation process that usually is associated with significant spectra changes (*i.e.* red shift) and chemical shift in NMR titration experiments.[14] However, based on the titration experiments of **1c**, no data has been obtained to support the deprotonation process.

To evaluate the selectivity of **1c**, 1 equiv of F^-, Cl^-, Br^-, I^-, AcO^-, $H_2PO_4^-$, NO_3^-, and HSO_4^- (added as their tetrabutylammonium salts) was incubated individually with **1c** (5.0×10^{-6} M) in CH_2Cl_2 at room temperature. The emission spectra at 442 nm were investigated with an excitation at 344 nm. As shown in the Fig. 3, **1c** displayed substantial fluorescence quenching (94%) in the presence of F^-, indicating a submicromolar binding affinity. In contrast, only a slight fluorescence decrease (less than 7%) was observed upon addition of Cl^-, Br^-, I^-, NO_3^-, or HSO_4^-. Although AcO^- and $H_2PO_4^-$ resulted in 15% and 24% quenching respectively, it was much smaller than the quenching observed from F^-. These results showed the high selectivity of **1c** for F^- over other competitive anions, indicating

that **1c** represented a robust sensor for high-throughput measurements against F^-.

In summary, we report a new fluorescence sensor (**1c**) based on *N*-imidazolyl-1,8-naphthalimide for the detection of fluoride with high sensitivity and selectivity. **1c** displays strong fluorescence due to coplanar geometry formed by the intramolecular H-bond between naphthalimide and imidazole moieties. The addition of F^- disrupts the H-bond and consequently causes significant fluorescence quenching. This sensing strategy provides a new "on–off" signal transition mechanism for fluorescence sensing on the basis of 1,8-naphthalimide.

This research is supported by Nebraska EPSCoR, URCA and URF in University of Nebraska at Kearney. Authors thank Professor Gene Wubbles in University of Nebraska at Kearney for many useful discussions and suggestions.

Notes and references

1 (*a*) P. d. Beer and P. A. Gale, *Angew. Chem., Int. Ed.*, 2001, **40**, 486–516; (*b*) C. R. Wade, A. E. J. Broomsgrove, S. Aldridge and F. P. Gabbaï, *Chem. Rev.*, 2010, **110**, 3958–3984.

2 J. R. Lakowicz, *Principles of Fluorescence Spectroscopy*, Springer, New York, 3rd edn, 2006.

3 (*a*) D. A. Jose, D. K. Kumar, B. Ganguly and A. Das, *Org. Lett.*, 2004, **6**, 3445–3448; (*b*) G. Xu and M. A. Tarr Wu, *Chem. Commun.*, 2004, 1050–1051; (*c*) J. Wu, J. Zhou, P. Wang, X. Zhang and S. Wu, *Org. Lett.*, 2005, **7**, 2133–2136; (*d*) E. J. Jun, K. M. K. Swamy, J. Bang, S. Kim and J. Yoon, *Tetrahedron Lett.*, 2006, **47**, 3103–3106; (*e*) R. M. F. Batista, E. Oliverira, S. P. G. Costa, C. lodeiro and M. M. M. Raposo, *Org. Lett.*, 2007, **9**, 3201–3204; (*f*) Q. Lu, L. Dong, J. Zhang, J. Li, L. Jiang, Y. Huang, S. Qin, C. Hu and X. Yu, *Org. Lett.*, 2009, **11**, 669–672; (*g*) S. V. Bhosale, S. V. Bhosale, M. B. Kalyankar and S. J. Langford, *Org. Lett.*, 2009, **11**, 5418–5421; (*h*) Y. Lin and C. Chen, *Org. Lett.*, 2009, **11**, 4858–4861; (*i*) Y. Kim, M. Kim and F. P. Gabbaï, *Org. Lett.*, 2010, **12**, 600–602; (*j*) S. Guha and S. Saha, *J. Am. Chem. Soc.*, 2010, **132**, 17674–17677; (*k*) R. Hu, J. Feng, D. Hu, S. Wang, S. Li, Y. Li and G. Yang, *Angew. Chem., Int. Ed.*, 2010, **49**, 4915–4918; (*l*) Q. Wang, Y. Xie, Y. Ding, X. Li and W. Zhu, *Chem. Commun.*, 2010, **46**, 3669–3671; (*m*) G. Li, W. Gong, J. Ye, Y. Lin and G. Ning, *Tetrahedron Lett.*, 2011, **52**, 1313–1316; (*n*) X. He and V. W. Yam, *Org. Lett.*, 2011, **13**, 2172–2175; (*o*) J. F. Zhang, C. S. Lim, S. Bhuniya, B. R. Cho and J. S. Kim, *Org. Lett.*, 2011, **13**, 1190–1193; (*p*) P. Rajamalli and E. Prasad, *Org. Lett.*, 2011, **13**, 3714–3717.

4 (*a*) V. Bhalla, H. Singh and M. Kumar, *Org. Lett.*, 2010, **12**, 628–631; (*b*) Y. Qu, J. Hua and H. Tian, *Org. Lett.*, 2010, **12**, 3320–3323; (*c*) Y. Li, J. Shao, X. Yu, X. Xu, H. Lin, Z. Cai and H. Lin, *J. Fluoresc.*, 2010, **20**, 3–8.

5 (*a*) B. M. Aveline, S. Matsugo and R. W. Redmond, *J. Am. Chem. Soc.*, 1997, **119**, 11785–11795; (*b*) Z. Xu, Y. Xiao, X. Qian, J. Cui and D. Cui, *Org. Lett.*, 2005, **7**, 889–892; (*c*) S. Paudel, P. Nandhikonda and M. D. Heagy, *J. Fluoresc.*, 2009, **19**, 681–691.

6 (*a*) V. Wintgens, P. Valat, J. Kossanyi, A. Demeter, L. Biczók and T. J. Bérces, *J. Photochem. Photobiol., A*, 1996, **93**, 109–117; (*b*) R. Parkesh, T. C. Lee and T. Gunnlaugsson, *Tetrahedron Lett.*, 2009, **50**, 4114–4116; (*c*) E. B. Veale, D. O. Frimannsson, M. Lawler and T. Gunnlaugsson, *Org. Lett.*, 2009, **11**, 4040–4043; (*d*) Z. Zhou, M. Yu, H. Yang, K. Huang, F. Li, T. Yi and C. Huang, *Chem. Commun.*, 2008, 3387–3389.

7 (*a*) P. Valat, V. Wintgens, J. Kossanyi, L. Biczók, A. Demeter and T. Bérces, *J. Am. Chem. Soc.*, 1992, **114**, 946–953; (*b*) D. Yuan and R. G. Brown, *J. Phys. Chem. A*, 1997, **101**, 3461–3466; (*c*) S. Saha and A. Samanta, *J. Phys. Chem. A*, 2002, **106**, 4763–4771; (*d*) H. Cao, T. McGill and M. D. Heagy, *J. Org. Chem.*, 2004, **69**, 2959–2966; (*e*) Y. A. Mednykh, Y. A. Manaev, V. V. Volchkov and B. M. Uzhinov, *Russ. J. Gen. Chem.*, 2004, **74**, 1728–1733; (*f*) F. Li, J. Cui, L. Guo, X. Qian, W. Ren, K. Wang and F. Liu, *Bioorg. Med. Chem.*, 2007, **15**, 5114–5121.

8 (*a*) T. Gunnlaugsson, P. E. Kruger, P. Jensen, F. M. Pfeffer and G. M. Hussey, *Tetrahedron Lett.*, 2003, **44**, 8909–8913; (*b*) D. Esteban-Gómez, L. Fabbrizzi and M. Licchelli, *J. Org. Chem.*, 2005, **70**, 5717–5720; (*c*) D. Srikun, E. W. Miller, D. W. Domaille and C. J. Chang, *J. Am. Chem. Soc.*, 2008, **230**, 4596–4597; (*d*) N. Singh, N. Kaur, B. McCaughan and J. F. Callan, *Tetrahedron Lett.*, 2010, **51**, 3385–3387; (*e*) B. Zhu, X. Zhang, H. Jia, Y. Li, H. Liu and W. Tan, *Org. Biomol. Chem.*, 2010, **8**, 1650–1654; (*f*) R. M. Duke, E. B. Veale, F. M. Pfeffer, P. E. Kruger and T. Gunnlaugsson, *Chem. Soc. Rev.*, 2010, **39**, 3936–3953.

9 H. Cao, D. I. Diaz, N. DiCesare, J. R. Lakowicz and M. D. Heagy, *Org. Lett.*, 2002, **4**, 1503–1505.

10 A. T. Peters and Y. S. S. Behesti, *J. Soc. Dyers Colour.*, 1989, **105**, 29–35.

11 Quantum chemical calculations were carried out by using Spartan 04 (v.1.0.3) at the Hartree–Fock/6-31G* level.

12 H. Cao, V. Chang, R. Hernandez and M. D. Heagy, *J. Org. Chem.*, 2005, **70**, 4929–4934.

13 P. Thordarson, *Chem. Soc. Rev.*, 2011, **40**, 1350–1323.

14 (*a*) D. Estebann-Gómez, L. Fabbrizzi and M. Licchelli, *J. Org. Chem.*, 2005, **70**, 5717–5720; (*b*) B. Liu and H. Tian, *J. Mater. Chem.*, 2005, **15**, 2681–2686; (*c*) X. Peng, Y. Wu, J. Fan, M. Tian and K. Han, *J. Org. Chem.*, 2005, **70**, 10524–10531; (*d*) H. Chen, H. Lin, Z. Cai and H. Lin, *Indian J. Chem.*, 2007, **46A**, 748–754.

