Pergamon

Tetrahedron Letters 43 (2002) 2991–2994

TETRAHEDRON LETTERS

4-Amino-1,8-dicyanonaphthalene derivatives as novel fluorophore and fluorescence switches: efficient synthesis and fluorescence enhancement induced by transition metal ions and protons

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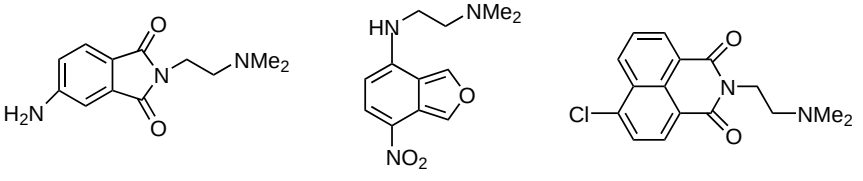
Received 23 October 2001; revised 20 February 2002; accepted 28 February 2002

Abstract—A new electronic push–pull fluorophore, 4-amino-1,8-dicyanonaphthalene, and its derivatives have been synthesized efficiently. They can be used as photo-induced electron transfer fluorescence switches which exhibit considerable fluorescence enhancement induced by transition metal ions Cr^{3+} and Fe^{3+} and also respond to pH values very sensitively. © 2002 Published by Elsevier Science Ltd.

Currently, much attention is being paid to fluorescent switches because of their application as highly effective sensors,[1] biological probes[2] and their possible application as molecular devices in information processing.[3,4] Photo-induced electron transfer[1] (PET) is the most commonly explored mechanism in the design and development of fluorescent switches. de Silva[1] indicated that PET fluorescent switches are generally multi-component systems containing a fluorophore as the signalling moiety, a receptor (usually, a substituted amine with an unbound electron pair) as the guest binding site, and a spacer to connect the fluorophore and the receptor. The PET interaction between fluorophore and receptor quenches ('switches off') the fluorescence. The 'switch on' state of fluorescence takes place in the presence of a guest, e.g. a proton, because the electron pair of the receptor nitrogen atom is tied up by the guest, which turns off the PET between fluorophore and receptor.

Researchers have focused on the design of PET sensors for H^+, alkaline metal ions, and alkaline-earth metal ions. They often use known fluorophores,[1] such as anthracene, naphthalimide, coumarin, etc. and a dialkylamine as receptor or a relatively complicated aza crown ether as a selective receptor.[1] But, much less attention has been paid to PET fluorescence sensors for transition metal ions, and there have been fewer reports on fluorescence enhancement (FE) induced by transition metal ions because of their fluorescence-quenching nature.[1] However, Samanta et al.[5–7] recently suggested that electron-deficient fluorophores could be employed to tune down the fluorescence quenching interaction between fluorophore and transition metal ions, so that strong fluorescence will be switched on when the receptor binds a transition metal ion. So far, only sensors using the known fluorophores, such as **A1**, **A2** and **A3**, have been successfully used as PET sensors for transition metal ions (Scheme 1).



A1 **A2** **A3**

Scheme 1. Some reported PET fluorescence sensors for transition metal ions.

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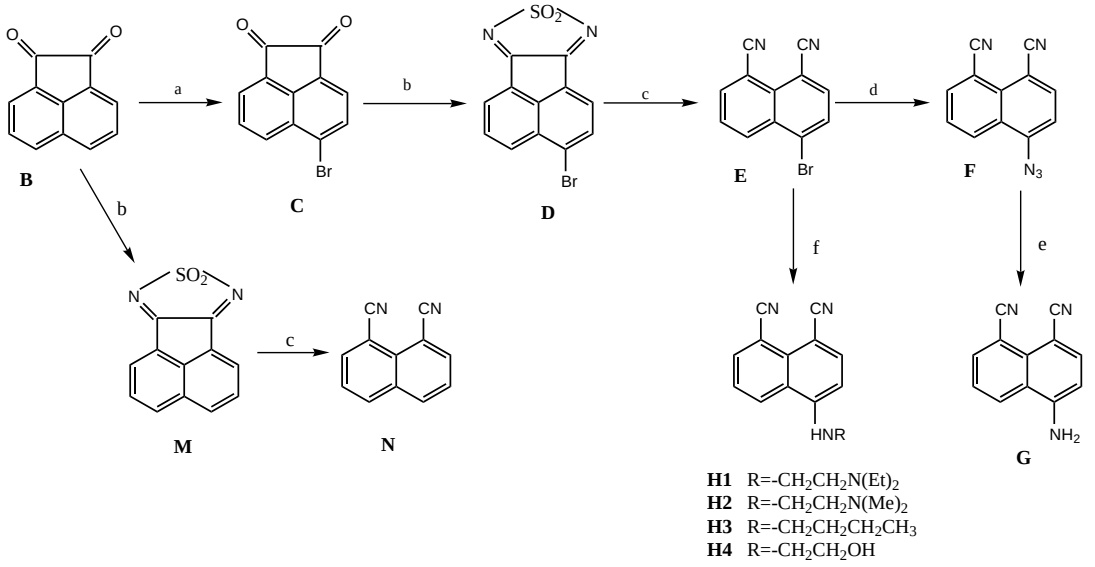
PII: S0040-4039(02)00441-0

As far as we know, no novel fluorophore specially designed for signalling recognition of transition metal cations has been reported. In fact, not since 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (BODIPY)[8] appeared in 1968 as a fluorophore precursor, no novel fluorophore system has been explored. In this paper, we report a new push–pull and electron-deficient fluorophore precursor 4-amino-1,8-dicyanonaphthalene (ADCN, compound **G**). In our design, with the two strongly electron-pulling cyano groups and an electron-pushing amino group incorporated at the 1-, 8- and 4-positions of the naphthalene ring, respectively, ADCN is an intramolecular charge transfer (ICT[1]) system, for which it should be possible to emit strong fluorescence. Compared with the established 4-amino-1,8-naphthalimide fluorophore (which has been used as a fluorophore in PET fluorescent probes for acidic organelles in biological systems[2]), ADCN has advantages such as its smaller size, better solubility, higher polarity, and greater electron-deficiency, which can be ascribed to the two cyano groups. Derived from this novel fluorophore precursor, fluorescence switches (compounds **H1** and **H2**) were designed by conversion of the primary amine to a dialkylamine receptor with an ethylene linker, which has proved to be the optimum 'spacer' unit for many 'fluorophore-spacer-receptor' PET fluorescence sensor families.[5–7,9,10]

Several of the reported syntheses[11–13] of 1,8-dicyanonaphthalene are inconvenient or low yielding and the reports on the synthesis of derivatives of 1,8-dicyanonaphthalene are also rare, perhaps because of difficulties with the synthesis. The following synthesis (Scheme 2) of 1,8-dicyanonaphthalene and its 4-bromo- and 4-(substituted)amino derivatives provides access to this family of compounds. From the starting material, acenaphthenequinone, via ring closure[14] (step b) catalyzed by dry HCl in ethanol for 30 min at reflux temperature, and thermal decomposition[13] (step c) in diethylene glycol diethyl ether for only 10 min at reflux temperature, 1,8-dicyanonaphthalene was obtained in a good yield. Step c was easy to control and was carried out under very mild conditions, resulting in less overheating than for the reported method in which solid substrates were heated with a metal bath to temperatures as high as 250°C in a closed vessel.[13] Similarly, if the starting material was 5-bromoacenaphthenequinone,[15] 4-bromo-1,8-naphthalene (compound **E**) was also obtained in good yield. The novel fluorophore **G** was synthesized from the intermediate **F** via substitution of the 4-bromo group with azide and reduction. It is worth noting that $NaBH_4$ as the reducing agent reduced the azide group to an amine with high yield and high selectivity without any effect on the cyano groups, which are reduced if other reducing agents such as $LiAlH_4$ are used. This observation may be valuable for other reductions in which cyano compounds are involved. The PET fluorescence switches **H1** and **H2** and other derivatives of ADCN, such as the reference compounds **H3** and **H4**, were obtained via substitution of the 4-bromo group with the corresponding amines. The products were identified using ^1H and ^{13}C NMR, MS, IR, elemental analysis, etc.[16]

As shown in Table 1, the fluorescence quantum yield (ϕ_F) of ADCN (**G**) in the moderately polar solvent, dichloromethane, was 0.66, which is high enough for a fluorophore precursor. In the highly polar solvent ethanol, the fluorescence quantum yield of ADCN decreased to 0.190, which is often observed for fluorophores with strong ICT interactions, and similar phenomena have been described.[1] The alkyl substituted derivatives of ADCN, such as **H3**, also exhibited similar solvatochromism to ADCN and emitted stronger fluorescence because of the electron-pushing effect of the alkyl groups. In dichloromethane, absorption and



Scheme 2. Synthesis of derivatives of 1,8-dicyanonaphthene: (a) liquid bromine, 60°C, 2 h, 80% yield; (b) sulfamide, EtOH, dry HCl, reflux, 30 min, 93% yield; (c) diethylene glycol, diethyl ether, reflux 10 min, 85% yield; (d) NaN_3, DMSO, 100°C, 5 min, 94% yield; (e) $NaBH_4$, THF, reflux 1 h, 80% yield; (f) the corresponding amine, pyridine, K_2CO_3, reflux 3–4 h, 70–80% yield.

Table 1. Spectroscopic data of ADCN derivatives

	G		H1		H2		H3		H4	
	CH_2Cl_2	EtOH	CH_2Cl_2	EtOH	CH_2Cl_2	EtOH	CH_2Cl_2	EtOH	CH_2Cl_2	EtOH
λ_{abs} (nm)	371	392	395	398	392	396	393	401	388	398
Log ε	4.11	4.14	4.02	4.11	3.89	3.93	4.18	4.25	4.27	4.27
λ_{em} (nm)	456	488	467	486	473	489	470	486	471	493
ϕ_F	0.660	0.190	0.645	0.031	0.592	0.052	0.738	0.197	0.709	0.544

fluorescence spectra of compounds **H1**, **H2** and **H4** were similar to those of **H3**. However, in ethanol, **H1** and **H2** exhibited unusually low fluorescence quantum yields, which was a clear indication of a PET interaction with a much higher rate in the polar solvent.[17,18] But, in ethanol, the fluorescence quantum yield of **H4** was much higher than that of **H3**, indicating that there was no PET fluorescence-quenching interaction for **H4**. The reason for this is that oxygen is not such a good electron-donor for PET as nitrogen (the oxidation potential of a hydroxyl group is much higher than that of a bisalkylamino group).[9,10] This also shows that the incorporation of a hydroxyl group increased the electron-pushing ability of the alkyl chain and the polarity of the whole molecule, so that in a solvent of high polarity, the excited state of **H4** was more stable, which resulted in strong fluorescence. The description above accords with our previous observations of 4-amino-1,8-naphthalimide derivatives,[10] which have been used by de Silva to design naphthalimide PET sensors.[9]

The influence of transition metal ions on the fluorescence of **H1** or **H2** was sharply different from that on the reference compound **H3**. Fluorescence of **H3** was quenched slightly without an observable wavelength shift in ethanol when the strongly fluorescence-quenching transition metal ions Cr^{3+}or Fe^{3+} were added. This implied that there was no strong interaction between the novel fluorophore and the transition metal ions. However, as illustrated in Fig. 1, in the absence of transition metal salts, **H1** has very weak fluorescence in anhydrous ethanol ($\phi_F = 0.03$), as expected for a good PET fluorescence switch. Interestingly, when different amounts of transition metal salts were added, considerable fluorescence enhancement (FE) was observed, the highest FE for Cr^{3+} (50 μM) and Fe^{3+} (50 μM) being 22- and 26-fold, respectively. A blue shift of about 20 nm for the fluorescence spectra in the presence of either of these ions indicated that the switch might bind metal ions via a bidentate chelation[19] with both nitrogen atoms of the receptor and aromatic amine. This chelation had two different effects. On the one hand, the photo-induced electron transfer from the receptor amine to the fluorophore was inhibited, which resulted in fluorescence enhancement. On the other hand, the aromatic amines' electron-donating effect for the push–pull fluorophore was weakened, and so, the spectra shifted to shorter wavelength. For **H2**, similar results were obtained: the fluorescence enhancement induced by transition metal ions was also remarkable, the highest FE being 15 and 18 fold for Cr^{3+} (50 μM) and Fe^{3+} (50 μM), respectively. Thus, our plans for designing these fluorescence sensors for transition metal ions were justified. The good performance of the sensor can be ascribed to the electron-deficient structure of ADCN, in which the two cyano groups played a critical role.

The pH sensitivity of this PET fluorescent sensor was also studied for the sake of exploring its potential application to detect protons in a microenvironment. As shown in Fig. 2, **H1** and **H2** responded differently to pH with very high sensitivity: when the pH was changed from 12 to 3, there was a 57-fold fluorescence enhancement for **H1** and a 35-fold enhancement for **H2**. The pH dependence of the fluorescence quantum

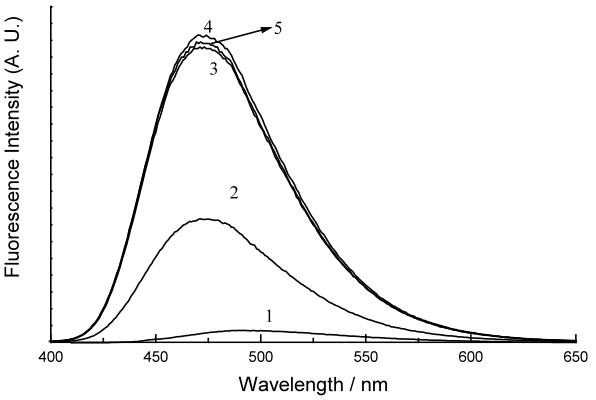


Figure 1. Fluorescence spectra of **H1** (μM) in EtOH in the presence of various amounts of Cr^{3+} (excited at 380 nm). The concentration of Cr^{3+} (μM): (1) 0; (2) 25; (3) 50; (4) 75 and (5) 100.

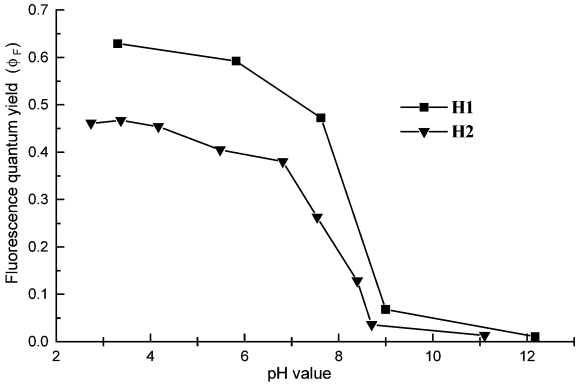


Figure 2. The influence of pH on fluorescence of compounds **H1** and **H2** in a solution of methanol and water (1:4).

yield can be analyzed according to the following equation:[9] $\log[(\phi_{Fmax}-\phi_F)/(\phi_F-\phi_{Fmin})]=pH-pK'_a$, the pK'_a values of the fluorescence switches **H1** and **H2** being 8.0 and 7.7, respectively.

In summary, we have designed a new fluorophore, 4-amino-1,8-dicyanonaphthalene (ADCN), and its derivatives **H1** and **H2** which respond to transition metal ions and protons sensitively. Further studies on their application in chemical biology and the structure–property relationships of the amino-dicyanonaphthalene derivatives are currently under investigation.

Acknowledgements

The National Natural Science Foundation of China, The Ministry of Education of China and Shanghai Foundation of Science and Technology financially supported this study.

References

1. de Silva, A. P.; Gunatatne, H. Q. N.; Gunnlauggson, T.; Huxley, A. J. M.; McCoy, C. P.; Radmancher, J. T.; Rice, T. E. *Chem. Rev.* **1997**, *97*, 1515–1566.
2. Haugland, R. P. *Molecular Probes*; Molecular Probes: Netherlands, 1996; pp. 278–279.
3. de Silva, A. P.; Gunatatne, H. Q. N.; McCoy, C. P. *J. Am. Chem. Soc.* **1997**, *119*, 7891–7892.
4. Lehn, J. M. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1304–1319.
5. Ramachamdram, B.; Sankaran, N. B.; Karmakar, R.; Saha, S.; Samanta, A. *Tetrahedron* **2000**, *56*, 7041–7044.
6. Ramachamdram, B.; Samanta, A. *Chem. Phys. Lett.* **1998**, *290*, 9–16.
7. Ramachamdram, B.; Saroja, G.; Sankaran, N. B.; Samanta, A. *J. Phys. Chem. B* **2000**, *104*, 11824–11832.
8. Treibs, A.; Kreuzer, F.-H. *Liebigs Ann. Chem.* **1968**, *718*, 208–223.
9. de Silva, A. P.; Gunatatne, H. Q. N.; Lynch, P. L. M.; Patty, A. J.; Spence, G. L. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1611–1616.
10. Qian, X.; Zhu, Z.; Chen, K. *Dyes Pigments* **1989**, *11*, 13–20.
11. Chang, S. *Synth. Commun.* **1982**, *12*, 673–680.
12. Nakayama, J.; Segiri, T.; Ohya, R. *J. Chem. Soc., Chem. Commun.* **1980**, 791–792.
13. Ege, G.; Beisiegel, E. *Synthesis* **1974**, 22–23.
14. Wright, J. B. *J. Org. Chem.* **1964**, *29*, 1905–1909.
15. Rule, H. G.; Thompson, S. B. *J. Chem. Soc.* **1937**, 1761–1763.
16. Compound **G**: Mp 270–272°C; ^{1}H NMR (400 MHz, DMSO-*d*) δ 6.79–6.81 (d, J=8.4 Hz, 1H), 7.56–7.60 (t, J=8.4 Hz, 1H), 7.84–7.86 (d, J=8.4 Hz, 1H), 8.16–8.18 (d, J=7.2 Hz, 1H), 8.55–8.57 (d, J=8.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) 90.22, 106.65, 107.85, 116.97, 118.45, 121.16, 123.77, 129.00, 130.24, 137.98, 139.37, 151.19; ESI–MS $[M+H]^+$ (m/z 194), $[M+NH_4]^+$ (m/z 211), $[M+Na]^+$ (m/z 216), $[M+K]^+$ (m/z 232), $[2M+NH_4]^+$ (m/z 404), $[2M+Na]^+$ (m/z 409), $[2M+K]^+$ (m/z 452); IR (KBr) 3369, 3232, 2216, 1579, 1521.
Compound **HHH1**: Mp 128.2–128.4°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08–1.11 (t, J=7.1 Hz, 6H, CH_3), 2.62–2.66 (q, J=7.8 Hz, 4H, CH_2CH_3), 2.88–2.90 (t, J=5.8 Hz, 2H, $NHCH_2CH_2NEt_2$), 3.29–3.32 (q, J=5.5 Hz, 2H, $NHCH_2CH_2NEt_2$), 6.46 (s, –N*H*–, 1H), 6.54–6.56 (d, J=8.9 Hz, 1H), 7.50–7.53 (t, J=7.6 Hz, 1H), 7.79–7.81 (d, J=8.3 Hz, 1H), 7.96–7.97 (d, J=7.21, 1H), 8.03–8.05 (d, J=8.55 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 12.64, 40.63, 46.94, 50.89, 93.89 104.93, 109.253, 117.95, 119.43, 123.00, 125.07, 126.70, 131.00, 137.85, 140.41, 149.02; ESI–MS m/z 292 (M^+); IR (KBr) 3361, 2219, 2206, 1581, 1531, 1342; $C_{18}H_{20}N_4$ Requires: C, 73.94; H, 6.89; N, 19.16. Found: C, 74.18; H, 6.79; N, 19.57%.
Compound **H2**: Mp 140–141°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 6H, CH_3), 2.66–2.69 (t, J=5.4 Hz, 2H, $CH_2N(CH_3)_2$), 3.22–3.26 (t, J=8 Hz, 2H, $HNCH_2$), 6.42–6.44 (d, J=8.4 Hz, 1H), 7.36–7.40 (t, J=8 Hz, 1H), 7.69–7.71 (d, J=8.8 Hz, 1H), 7.84–7.86 (d, J=7.6 Hz, 1H), 8.16–8.21 (d, J=8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 40.3, 44.82, 56.51, 92.89, 103.84, 108.10, 117.08, 118.52, 122.22, 124.12, 126.67, 130.17, 137.07, 139.51, 148.35; IR (KBr) 3384, 2948, 2821, 2219, 2206, 1581, 1540, 1340; ESI-MS $[M+H]^+$ (m/z 265).
Compound **H3**: Mp 226–227°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97–1.01 (t, J=7.6 Hz, 3H, CH_3), 1.45–1.51 (q, J=7.6 Hz, 2H, CH_2CH_3), 1.72–1.76 (t, J=7.2 Hz, 2H, $CH_2CH_2CH_3$), 3.32–3.35 (t, J=7.2 Hz, 2H, $NHCH_2$), 6.60–6.62 (d, J=8.4 Hz, 1H), 7.50–7.54 (t, J=8.4 Hz, 1H), 7.84–7.86 (d, J=8.4 Hz, 1H), 8.02–8.04 (d, J=7.2 Hz, 1H), 8.61–8.63 (d, J=8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 13.38, 19.76, 29.66, 42.72, 90.90, 102.92, 107.13, 116.80, 118.36, 121.95, 123.22, 127.65, 129.99, 136.66, 139.14, 148.81; IR (KBr) 3384, 2959, 2218, 1579, 1333; ESI–MS $[M+H]^+$ (m/z 250), $[M+NH_4]^+$ (m/z 267), $[M+Na]^+$ (m/z 272).
Compound **H4**: Mp 224–225°C; ^{1}H NMR (400 MHz, DMSO-*d*) δ 3.39–3.44 (q, J=5.6 Hz, 2H, $NHCH_2$), 3.65–3.68 (t, J=6 Hz, 2H, CH_2OH), 6.76–6.78 (d, J=8.8 Hz, 1H), 7.62–7.66 (t, J=8.4 Hz, 1H), 7.96–7.98 (d, J=8.4 Hz, 1H), 8.21–8.23 (d, J=7.6 Hz, 1H), 8.67–8.69 (d, J=8.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-*d*) 45.62, 58.58, 90.28, 103.74, 106.68, 117.05, 118.49, 121.89, 124.18, 128.41, 129.92, 137.84, 139.89, 149.40 IR (KBr) 3380, 3357, 2219, 1585, 1546, 1340; ESI–MS $[M+H]^+$ (m/z 238), $[M+Na]^+$ (m/z 270), $[2M+H]^+$ (m/z 475).
17. Kavarnos, G. J.; Turro, N. J. *Chem. Rev.* **1986**, *86*, 401–449.
18. Poteau, X.; Brown, A. I.; Brown, R. G.; Holmes, C.; Mathew, D. *Dyes Pigments* **2000**, *47*, 91–105.
19. Ramachandram, B.; Samanta, A. *J. Phys. Chem. A* **1998**, *102*, 10579–10587.