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Novel naphthalimide derivatives with near-infrared emission: synthesis via photochemical cycloaromatization, fluorescence in solvents and living cell

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ABSTRACT

In this Letter, a pair of novel naphthalimide derivatives with long-wavelength emission (>600 nm) and larger Stokes shift (>140 nm) have been developed through the photochemical cycloaromatization, in which intramolecular radical-induced 1,3-aromatic hydrogen transfer might be occurred. Cell uptake experiments showed that dye **2** could be used as a potential NIR fluorescence imaging agent.

The operational light input/output wavelengths of most current biological indicators are in the range of 300–600 nm, which often limits their use as biological sensors or as reagents for photodynamic therapy, because this spectral region suffers from strong interference due to the background absorbance and auto-fluorescence from biological environment or endogenous chromophores in sample media. So, it has aroused much attention to develop new near-infrared fluorescent dyes as powerful detecting or treating tools in biological systems.[1,2]

Many researchers have used heptamethine cyanine dyes as fluorescent labels or sensors for biomolecules in vivo, because their spectra can reach near-infrared (NIR) region. However, polymethine cyanine dyes are not so easy to be synthesized and modified, their photo-stabilities are relatively low and their Stokes shift is usually less than 25 nm, which may cause self-quenching and measurement error by the exciting and scattered light, and then decreases the detection sensitivity to a great extent. Therefore, NIR dyes with a larger Stokes shift are very promising for NIR fluorescence bioassays. 1,8-Naphthalimide is a famous fluorophore with high stability.[3] It can be easily modified by interacting with other biomolecules at their imide moiety. Many of their derivatives have good photostability, high fluorescence quantum yield [3,4] and have been widely used as labels or probes for proteins, cells, lysosomes and other acidic organelles.[5,6] However, the emission bands of most naphthalimide derivatives are in blue and green-yellow regions.[7] Although it was known that electron-donating groups at the 4,5-positions of 1,8-naphthalimides usually increase the fluorescence quantum yield of the compounds and shift the emission to long wavelength,[8] the reports on 1,8-naphthalimides derivatives with emission wavelengths longer than 600 nm are very few. Therefore, it motives us to prepare NIR dyes **1** and **2** through photosensitive radical cyclization.

Starting from compound **3,** *N*-butyl-4-bromo-5-nitro-1,8-naphthalimide,[9] dye **1**[10] with methoxy group or dye **2**[10] with *N′,N*-dimethylamino-group were synthesized in four-step scheme, respectively. The details for the syntheses are shown in Scheme 1.

Photo-irradiation of compounds **6**[11] or **7**[12] was carried out at a wavelength of 300 nm in dry chloroform as well as in polar solvent such as acetonitrile. In all cases, the same product was obtained through the formation of five-membered fused carbocyclic structures. Peri-diacetylene **6** (or **7**), a yellow (blue-black) fluorescent solid, was prepared from *N*-butyl-4-bromo-5-iodo-1,8-naphthalimide **5,**[13] catalytic amounts of 2.5 mol % $Pd(PPh_3)_4$ and 5 mol % CuI in triethylamine at 90 °C. The synthesis of **5** from **4**[14] involved two steps: diazotization of *N*-butyl-4-bromo-5-amino-1,8-naphthalimide **4** in dilute hydrochloric acid and decomposition of the corresponding diazonium chloride in aqueous potassium iodide (67% yield).

When **6** (or **7**) was dissolved in dry chloroform and irradiated by the light with wavelength of 300 nm, dyes **1** (or **2**) was developed. In this photo-chemical reaction process, we speculated that 3-hydrocyclohexa-1,2,4-triene intermediate formed first through photochemical cycloaromatization, followed by a very rapid radical-induced 1,3-hydrogen transfer and thus resulted in a stable phenyl ring,[15–17] which involved a geometry change and hydrogen rearrangement as shown in Scheme 2. According to Balasubramaniyan's points,[18] this cyclization process may include the effects of concerted, dipolar and more complex reaction mechanisms, too. The other intermediates such as cyclobutadiene might also be formed during the photochemical process. We attempted to isolate the intermediates, but failed.

Radical-induced hydrogen migration was very common when the hydrogen was originated from an aliphatic hydrocarbon or from a heteroatom-bonded hydrogen, in which, unstable radical

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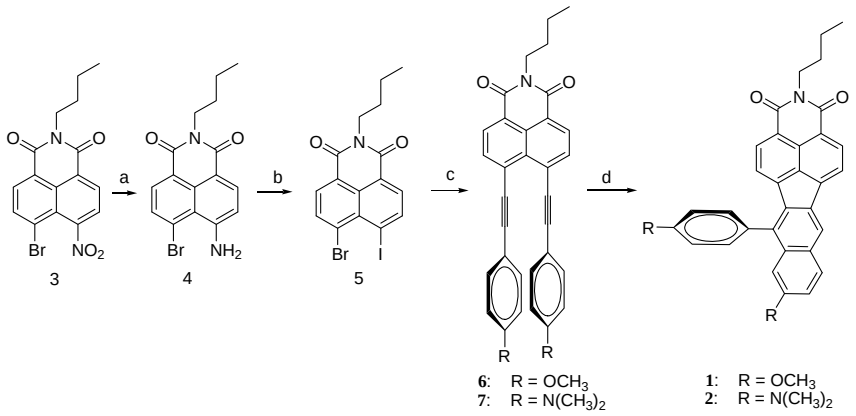
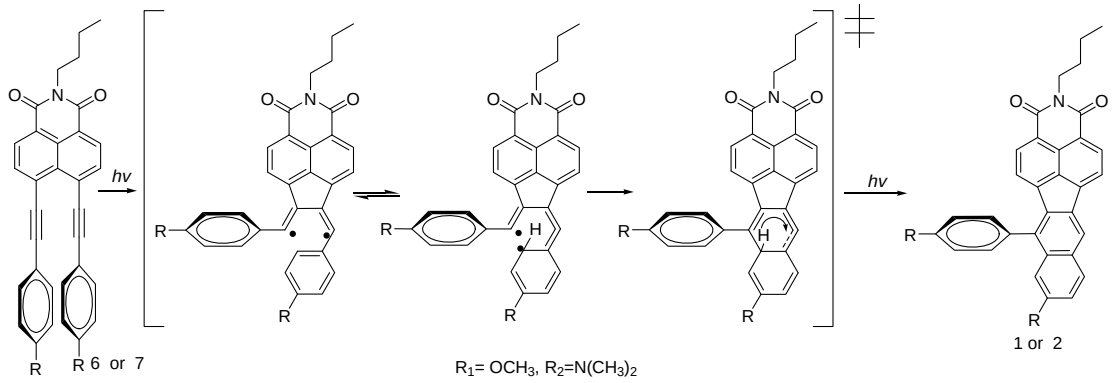


Scheme 1. Synthetic procedures of **1** and **2**. Reagents and conditions: (a) $SnCl_2{\cdot}2H_2O$, AcOH, HCl (g), room temperature, 90%; (b) $NaNO_2$, HCl, KI, 0–5 °C, 48%; (c) methoxyphenylethyne(4-*N*′,*N*-dimethylphenylethyne), $Pd(PPh_3)_4$, CuI, Et_3N, N_2, reflux, 85%; (d) *hν*, 30%.



Scheme 2. Possible mechanism of the product formation for the photoreactions of **6** or **7.**

formed initially, and then it rearranged rapidly to form a more stable aromatic compound. However, hydrogen migrations from an aromatic hydrocarbon are very difficult because aromatic hydrogen cannot easily be abstracted by radicals. For this reason, benzene is often used as solvent for free radical reactions. Up to now, only a few examples of radical-induced aromatic hydrogen transfer, for example, 1,5 or 1,6-hydrogen transfer were reported,[19,20] while the reports on 1,3 or 1,4-aromatic hydrogen transfer have not be found. This reaction process from compound **6** (or **7**) to dye **1** (or **2**) might provided the first example of radical-induced aromatic 1,3-hydrogen transfer.

Table 1 illustrates the photophysical data of dyes **1** and **2** in different solvents. It can be seen that when the polarity of solvent increases, a larger Stokes shift will increase, while their fluorescence quantum yields decrease. The largest Stokes shift and longest emission wavelengths for **1** and **2** are 136 nm, 620 nm and 166 nm, 750 nm, respectively. It means that **1** and **2** have potential application in biological environments.

Table 1
Spectroscopic data of **1** and **2** in different solvents

	Solvent	λ_{abs} (nm)	log ε	λ_{flu} (nm)	Φ_f
1	Dichloromethane	485	4.84	555	0.406
	Ethylacetate	480	4.80	561	0.400
	Methanol	484	4.71	620	0.145
2	Dichloromethane	580	5.08	721	0.095
	Ethylacetate	570	5.12	715	0.080
	Methanol	584	5.32	750	0.015

[a] Determined by comparison with rhodamine B in ethanol (Φ = 0.49, according to Ref. 21).

In the case of **1**, with a methoxy group attached to the *para* position of the benzene ring, the absorption and emission peaks in methanol were centred at 484 nm and 620 nm, respectively, and a high fluorescence quantum yield was obtained. The Stokes shift was in the range of 70–100 nm varied with solvent.

As for compound **2,** with dimethylamino group instead of methoxy, the absorption and emission maxima in methanol shifted to 584 nm and 750 nm, respectively. And its fluorescence quantum yield was much lower than that of **1**. The Stokes shift of **1** and **2** increases in the following order: dichloromethane ≈ ethyl acetate < methanol. It is explained that ICT dyes usually show an increase in Stokes shift with increasing solvent polarity. Compared with **1**, the dimethyl-amino group affected the photophysical properties of **2** in two ways: its strong electron-donating ability stabilized the highly polar excited state and the pre-twisted geometry come from steric hindrance between the *peri*-proton and *N*-methyl group favoured a further formation of the **TICT** state. The former made both emission and absorption maxima shift to longer wavelengths, and the latter led to a remarkable lower fluorescence quantum yield of **2** (less than 0.1). The photo-induced electron transfer (PET) from the diaminophenyl group to the fluorophore also quenched the fluorescence of **2**.[22] The remarkably large Stokes shift (more than 140 nm) for compound **2** suggested the possible occurrence of a TICT state from the donor moiety to the acceptor unit. On the other hand, according to Joertners energy gap law, when the energy of the emissive state is lowered, the non-radiative de-excitation processes increase exponentially, which results in the lower quantum yield of **2** (Fig. 1).

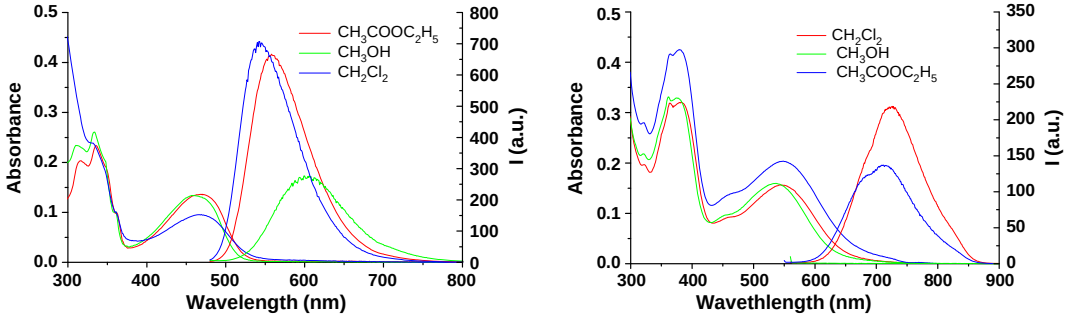


Figure 1. Absorption and emission spectra of **1** and **2** in different solvents (**1**: excited slit width 5 nm, emission slit width 5 nm; **2**: excited slit width 10 nm, emission slit width 10 nm).

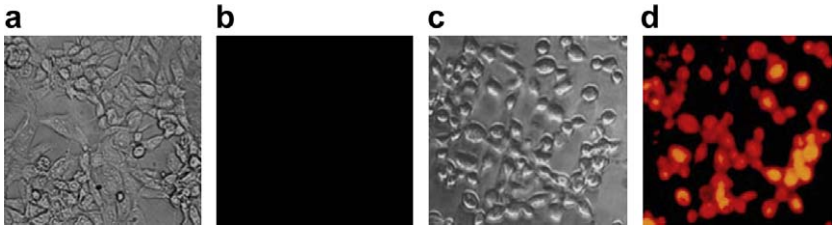


Figure 2. Fluorescence microphotographs of V79 cells incubated with (c, d) or without (a, b) 10 μM of **2** at 37 °C. Scanning was taken after 2 h incubation. Magnification was 1000×. (a) Brightfield image of cells; (b) excited at 537 nm, no obvious fluorescence was observed; (c) scanning was taken on brightfield; (d) excited at 537 nm.

V79 379A Chinese hamster cells were used for the evaluation of dye **2** as potential cell staining or imaging agent, which were maintained as exponentially growing suspension cultures in Eagle's minimal essential medium with Earle's salts, modified for suspension cultures with 7.5% fetal calf serum. The dye was added to cell suspensions to give the appropriate concentration at 10 μM. The images were taken with Leica DMIRB imaging system. As shown in Figure 2d, after incubation with dye **2** for 2 h at 37 °C, it showed an intense intracellular red fluorescence with the excitation wavelength at 537 nm (luminescence lifetimes 8 ms), which revealed that **2** could be potentially used as a biological label.

In summary, we provided two novel naphthalimide derivatives with near-infrared emission and large Stokes shift, which were synthesized through photo-induced cyclization by radical-induced 1,3-aromatic hydrogen transfer. Cell uptake experiments with fluorescence images implied the potentials of the long-wavelength fluorescent dye **2** used as a NIR fluorescence imaging agent.

Acknowledgements

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10. *Preparation of* **1** *and* **2**: The solution of **6** or **7** (50 mg) in dry chloroform was photo-irradiated by the light with wavelength of 300 nm for 10 min, then removed the solvent in vacuo. The residual materials were purified by column chromatography (SiO_2, $CHCl_3$: n-C_6H_{12} = 1:1) to give **1** as a yellow-red solid 15 mg (30%) (2 as blue-black solid 12 mg (25%).**1**: mp 175–176 °C, IR (KBr) v: 2918, 1691, 1654, 1632, 1606, 1502, 1450, 1350, 1220, 1175, 1027 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.97 (t, J = 7.2 Hz, 3H), 1.41–1.47 (m, 2H), 1.65–1.71 (m, 2H), 3.76 (s, 3H), 4.01 (s, 3H), 4.13 (t, J = 7.2 Hz, 2H), 6.94 (s, 1H), 7.20 (d, J = 8.4 Hz, 3H), 7.41 (d, J = 7.8 Hz, 2H), 7.85 (d, J = 8.8 Hz, 1H), 7.95 (d, J = 7.8 Hz, 1H), 8.20 (d, J = 8.8 Hz, 2H), 8.49 (d, J = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.85, 20.39, 30.48, 40.10, 55.29, 55.40, 107.15, 114.85, 118.75, 119.12, 121.26, 122.42, 122.50, 129.05, 129.54, 130.62, 130.74, 132.34, 134.03, 134.73, 135.64, 135.85, 137.03, 142.56, 142.92, 158.99, 159.67, 163.97, 164.09. HRMS (ESI^+) calcd. for $C_{34}H_{27}NO_4$ [M+H$^+$]: 514.2018, found: 514.2020. Compound **2:** mp. 180–181 °C, IR (KBr) v: 3414, 2918, 1691, 1651, 1606, 1517, 1450, 1342, 1231, 1112. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.975 (t, J = 7.2 Hz, 3H), 1.43–1.47 (m, 2H), 1.66–1.75 (m, 2H), 2.96 (s, 6H), 3.11 (s, 6H), 4.14 (t, J = 7.2 Hz, 2H), 6.79 (m, 2H), 7.01 (d, J = 8.4 Hz, 2H), 7.12 (d, J = 8.4 Hz, 1H), 7.33 (d, J = 8 Hz, 2H), 7.78 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 7.8 Hz, 1H), 8.10 (s, 1 H), 8.18 (d, J = 7.8 Hz, 1H), 8.50 (d, J = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.85, 20.41, 30.50, 40.04 40.67, 40.15, 48.59, 48.68, 113.00, 115.8, 118.29, 120.44, 122.30, 122.41, 125.66, 126.24, 127.27, 128.35, 129.30, 129.46, 129.58, 130.20, 130.30, 130.83, 131.05, 131.29, 132.36, 133.07, 133.43, 164.17, 164.28. HRMS (ESI^+) calcd for $C_{36}H_{33}N_3O_2$ [M+H$^+$]: 540.2636, found: 540.2642.
11. *Preparation of N-butyl-4,5-di(p-methoxy-phenylethynyl)-1.8-naphthalimide* (**6**): To a suspension of **5** (45 mg, 0.1 mmol) in triethylamine (10 mL) under N_2 atmosphere, CuI (0.0013 g, 0.007 mmol), $Pd(PPh_3)_4$ (0.0046 g, 0.4 mmol) and p-methoxyphenylethyne (40 mg, 0.3 mmol) were added. The reaction mixture was stirred for 6 h at reflux temperature. The suspension was filtered and

washed with ethyl acetate. The organic layer was washed with water, dried over anhydrous $MgSO_4$ and the solvent was removed in vacuo. The residual material was purified by column chromatography (SiO_2, $CHCl_3$) to give **6** as a yellow-red solid: 41 mg (80%) mp 155–156 °C. IR (KBr) *v*: 2946, 2177, 1580, 1506, 1387, 1354, 1250, 1086 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.99 (t, J = 7.2 Hz, 3H), 1.42–1.50 (m, 2H), 1.70–1.78 (m, 2H), 3.80 (s, 6H), 4.19 (t, J = 7.2 Hz, 2H), 6.72 (d, J = 8.0 Hz, 4H), 7.34 (d, J = 8.0 Hz, 4H), 8.02 (d, J = 7.8 Hz, 2H), 8.57 (d, J = 7.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.93, 20.59, 30.20, 40.46, 55.9, 92.91, 113.12, 117.87, 122.99, 125.28, 131.36, 131.89, 133.48, 133.77, 134.87, 160.24, 162.86, HRMS (ESI^+) calcd for $C_{34}H_{28}NO_4$ [M+H$^+$]: 514.2018, found: 514.2013.

12. *Preparation of N-butyl-4,5-di(p-N′,N-dimethylphenylethynyl)-1,8-naphthalimide* (**7**): Compound **7** was obtained by the same procedure with 5 and 4-*N*′,*N*-dimethylphenylethyne as raw material (85%). Mp: 162–163 °C, IR (KBr) *v*: 2925, 2200, 1688, 1651,1576, 1517, 1443, 1350, 1231, 1190, 1064 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.99 (t, J = 7.2 Hz, 3H), 1.44–1.51 (m, 2H), 1.70–1.78 (m, 2H), 2.98 (s,12H), 4.18 (t, J = 7.2 Hz, 2H), 6.54 (d, J = 8.0 Hz, 4H), 7.33 (d, J = 8.4 Hz, 4H), 7.97 (d, J = 8 Hz, 2H), 8.53 (d, J = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.83, 20.40, 30.20, 40.29, 88.32, 111.67, 121.25, 129.07, 130.46, 133.36, 133.76, 163.93, HRMS (ESI^+) calcd for $C_{36}H_{33}N_3O_2$ [M+H$^+$]: 540.2651, found: 540.2648.
13. *Preparation of N-butyl-4-bromo-5-iodo-1.8-naphthalimide* (**5**): 30 mL of $NaNO_2$ (1.6 g, 0.023 mmol) aqueous solution was dropwise added to the HCl (22%, 25 mL) aqueous solution of **4** (3.5 g, 0.01 mol) at 0 °C. The reaction mixture was stirred for 2 h at this temperature. The resulting precipitate was added to 40 mL of KI (8.85 g, 0.05 mol) aqueous solution and the mixture reacted for 1 h, after which added $NaHSO_3$ to destroy excessive I^-. The resulted solid was collected by filtration and then purified by column chromatography (SiO_2, $CHCl_3$) to give (**5**) as a white solid in 60% Yield (2.7 g), mp 165.1–166.4 °C, IR (KBr) *v*: 2950, 1695, 1647, 1630, 1560, 1430, 1280, 1150, 1035 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.985 (t, J = 7.2 Hz, 3H), 1.42–1.47 (m, 2H), 1.69–1.75 (m, 2H), 4.16 (t, J = 7.2 Hz, 2H), 8.18 (d, J = 8.0 Hz, 1H), 8.25 (d, J = 8.0 Hz, 1H), 8.41 (d, J = 8 Hz, 1H), 8.72 (d, J = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.83, 20.29, 30.20, 40.36, 107.12, 125.87, 126.67, 128.99, 135.28, 136.66, 136.87, 139.15, 139.87, 141.65, 161.56, 163.86, HRMS (ESI^+) calcd for $C_{16}H_{14}NO_2BrI$ [M+H$^+$]: 457.9253, found: 457.9264.
14. *Preparation of N-butyl-4-bromo-5-amino-1.8-naphthalimide* (**4**): Compound **3** (3.76 g, 0.01 mol) was added to a previously prepared solution of glacial acetic acid (40 ml) containing 15.3 g of $SnCl_2$ (0.08 mmol) and aerated with hydrogen chloride. The reaction mixture was stirred for 1 h. The precipitated solid was collected by filtration and washed with water. Crystallization from acetic acid gave **4** as yellow needles: 3.42 g (98.8%) mp 210.5–211.2 °C. IR (KBr) *v*: 3460, 3370, 1700, 1650, 1630, 1560, 1420, 1280, 1150, 1030. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.975 (t, J = 7.2Hz, 3H), 1.43–1.45 (m, 2H), 1.70–1.75 (m, 2H), 4.14 (t, J = 7.2 Hz, 2H), 6.20–6.40 (br s, 2H), 6.85 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 8.34 (d, J = 8 Hz, 1H), 8.42 (d, J = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.83, 20.38, 30.15, 40.12, 112.12, 112.16, 117.52, 122.74, 125.46, 131.56, 131.79, 132.49, 134.23, 150.52, 163.61, 164.01, HRMS (ESI^+) calcd for $C_{16}H_{16}N_2O_2Br$ [M+H$^+$]: 347.0395, found: 347.0386.
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