Synthesis and Fluorescence Tuning of Novel Nitroxides with a Binaphthyl Framework

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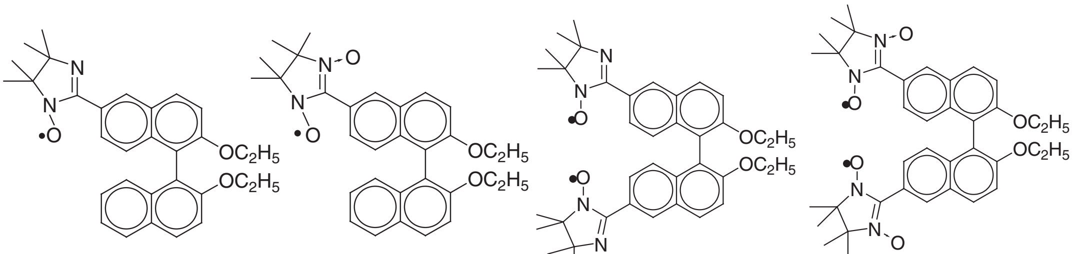
Four novel nitroxides were synthesized, and the fluorescence tuning of these molecules with the action of different chemical inputs was investigated; the results suggested that these nitroxides could serve as a redox fluorescence switch.

Fluorescence spectroscopy, fluorescence imaging, fluorescent sensors, and fluorescent probe techniques are powerful tools in analytical chemistry, molecular biology, biophysics, biochemistry, and medical diagnostics.[1] Therefore, functionalized molecules with fluorescent cores and receptor units have been intensively investigated.[2] Nitronyl nitroxides are a class of important functionalized molecules, which have characteristics of magnetism, anticancer, antiradiation, antioxidation, etc.[3] It has been found that nitroxide is a strong intramolecular quencher of the fluorescence from fluorophores. Hence, bonding of the nitroxide unit to a fluorescent core will lead to disappearance of fluorescence.[4] There are two possible ways of quenching the fluorescence: one due to the presence of nitroxide (Process A), and the other one owing to intramolecular charge transfer (ICT) from the imidazole unit to binaphthyl unit (Process B).[5] These two quenching processes can be arrested by reactions with suitable chemical reagents. Both reduction of nitroxide to hydroxylamine and protonation of nitroxide by acid are accompanied by the enhancement of fluorescence.[5] Therefore, molecules with fluorescent cores and nitroxide receptor can be used for fluorescent switches and as such, have attracted considerable interest in recent years.

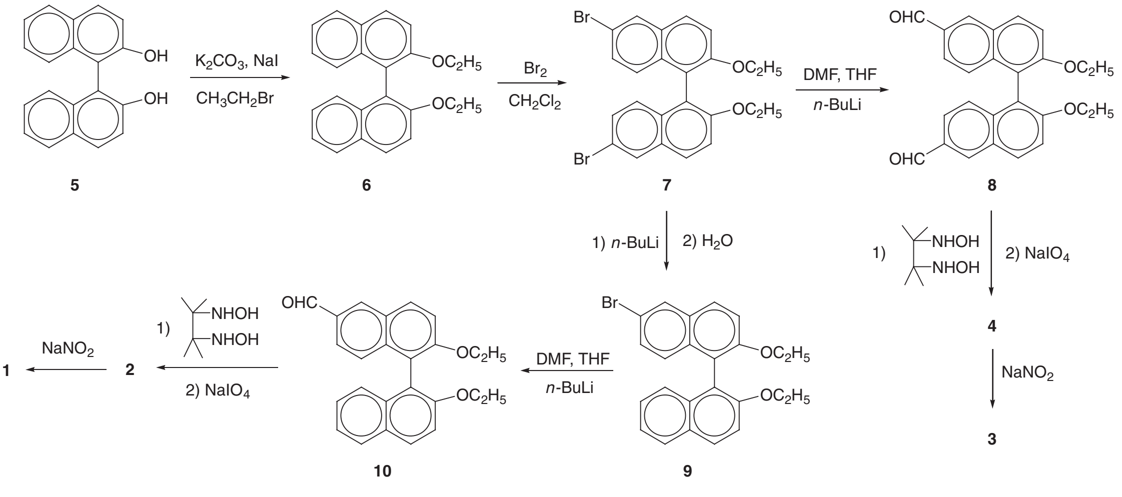
Herein we report the synthesis of four novel nitroxides **1**–**4** (Figure 1) and their fluorescence response to different chemical inputs. Nitroxides **1**–**4** were synthesized from binaphthol through multistep synthesis (Scheme 1).[6]

As expected, a solution of compound **1** shows rather weak fluorescence (curve *a* in Figure 2). Protonation of the nitroxides **1** will reduce the electron-donating ability, and hence the ICT reaction from the imidazole unit to binaphthyl will be arrested. For this purpose, CF_3COOH (TFA, 1.5×10^{-5} M) was added to the solution of **1** (1.5×10^{-6} M). But the fluorescence intensity was enhanced only slightly (curve *b* in Figure 2). Then mercaptan reductants including cysteine methyl ester hydrochloride (I) (1.5×10^{-4} M), 2-mercaptoethanol (II)



1 **2** **3** **4**

Figure 1. Structures of nitroxides **1**–**4**.



Scheme 1. Synthesis of nitroxides **1**–**4**.

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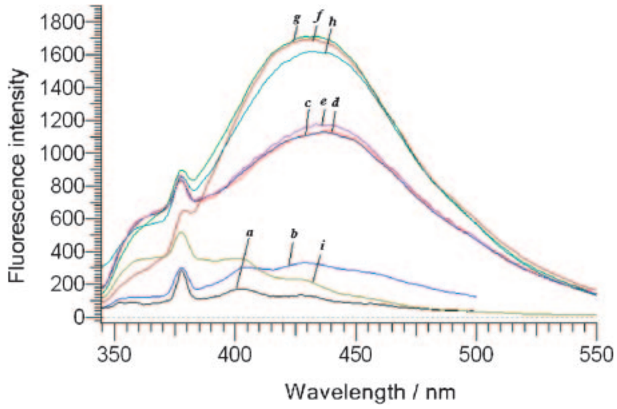

Figure 2. Fluorescence spectra of **1** in THF with an excitation wavelength of 340 nm upon different chemical inputs. (*a*) **1**, (*b*) **1** + TFA, (*c*) **1** + I, (*d*) **1** + II, (*e*) **1** + III, (*f*) **1** + TFA + I, (*g*) **1** + TFA + II, (*h*) **1** + TFA + III, and (*i*) the fluorescence recovered solution + $NaIO_4$ + Et_3N.

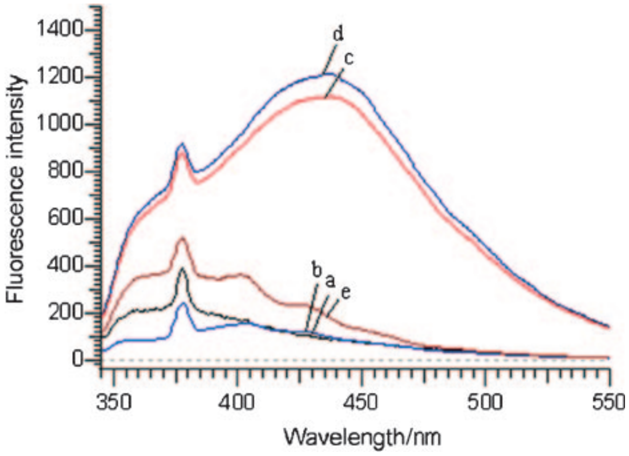

Figure 3. Fluorescence spectra of **2** in THF upon addition of different chemical reagents. (*a*) **2**, (*b*) **2** + TFA, (*c*) **2** + II, (*d*) **2** + TFA + II, and (*e*) the fluorescence recovered solution + $NaIO_4$ + Et_3N.

(1.5×10^{-4} M), and α-lipoic acid (III) (1.5×10^{-4} M) were added to the solution of **1** respectively in order to prohibit process A. The results showed that the fluorescence intensity of **1** increases dramatically to about 10 times the original value with the addition of mercaptan reductant (curves *c*, *d*, and *e* in Figure 2). This indicates that process A is more critical than process B for fluorescence recovery.

Next, we investigated the fluorescence spectral changes upon addition of acid and reductant together to the solution in order to block process A and process B together. The experimental results showed that the fluorescence intensity was enhanced further (curves *f*, *g*, and *h* in Figure 2). The fluorescence was quenched again when $NaIO_4$ and Et_3N were added to the above solution (curve *i* in Figure 2), which suggested that **1** could serve as a redox fluorescence switch.

For nitronyl nitroxide **2**, although the *N* atom of the imidazole cycle was coordinated with *O* atom, the ICT process was effective. Similar experiments were performed with **2** (using II as the reductant), and consistent fluorescence spectral changes were observed (Figure 3).

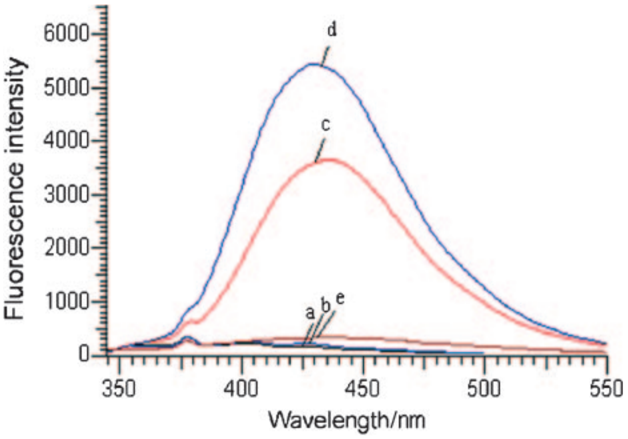

Figure 4. Fluorescence spectra of **3** in THF upon addition of different chemical reagents. (*a*) **3**, (*b*) **3** + TFA, (*c*) **3** + II, (*d*) **3** + TFA + II, and (*e*) the fluorescence recovered solution + $NaIO_4$ + Et_3N.

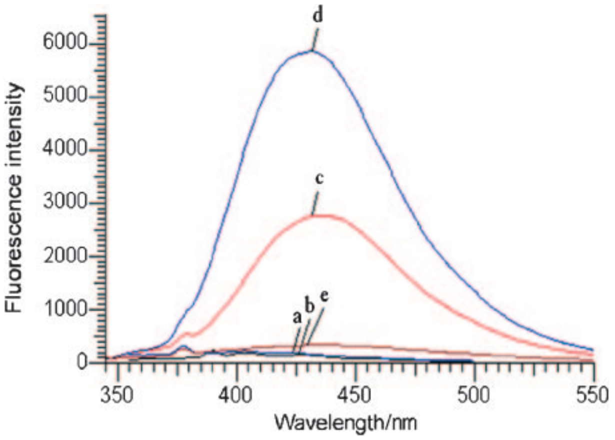

Figure 5. Fluorescence spectra of **4** in THF upon addition of different chemical reagents. (*a*) **4**, (*b*) **4** + TFA, (*c*) **4** + II, (*d*) **4** + TFA + II, and (*e*) the fluorescence recovered solution + $NaIO_4$ + Et_3N.

Compounds **3** and **4** contain two nitroxide receptor units. Addition either of II or of a mixture of TFA and II to a solution of **3** (or **4**) resulted in fluorescence enhancement more significant than that of **1** and **2** respectively (Figure 4 and Figure 5).

These data suggest that nitroxides containing two receptor units might serve as a redox switch with higher measure and are listed in Table 1.

In summary, four novel nitroxides **1–4** with a binaphthyl framework were synthesized, and the fluorescence tuning of these molecules with the action of different chemical inputs was investigated. Addition of TFA led to slight fluorescence recovery, while addition of mercaptan reductant induced the fluorescence recovery significantly. More significant fluorescence enhancement was observed under the combined action of the reductant and acid. Moreover, oxidant and organic base also effected fluorescence quenching. It is suggested that the fluorescence quenching effect of the nitroxide unit was dominant, and that the ICT effect was subsidiary. Additionally, nitroxides containing two receptor units (**3** and **4**) led to

Table 1. The Relative Fluorescence Quantum Yields (Φ) of **1**–**4** under Different Conditions[a)]

Nitroxides	Free radicals[b)]	Chemical inputs		
		TFA[c)]	II[d)]	TFA[c)] + II[d)]
1	0.0106	0.0158	0.277	0.370
2	0.0309	0.0224	0.241	0.319
3	0.0170	0.0136	0.438	0.629
4	0.0857	0.0713	0.590	0.767

a) Relative to quinine sulfate. b) 1.5×10^{-6} M in THF. c) 1.5×10^{-5} M. d) 1.5×10^{-4} M.

more significant fluorescence enhancement compared to single receptor unit nitroxides (**1** and **2**). Therefore, more nitroxide receptor units may be beneficial for improving the sensitivity of redox switches.

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Supporting Information

Experimental procedure and spectral data for the key derivatives. This material is available free of charge on the web at http://www.csj.jp/journals/bcsj/.

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