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Dual-mode fluorescence switching of photochromic bisthiazolylcoumarin†

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Three new photochromic coumarins were synthesized. Fluorescence of the open form of 7-hydroxy-3,4-bisthiazolyl-coumarin increased to 1400% by changing the pH only slightly from 6.05 to 7.58. This was subsequently quenched to 1.5% of the maximum intensity at the UV photostationary state in water–methanol media.

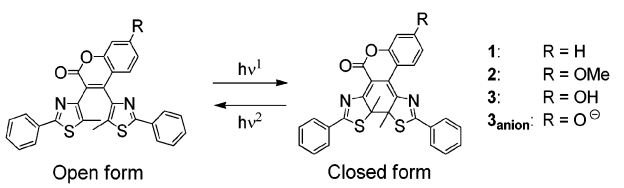
Photochromic compounds, which change their properties reversibly in response to light irradiation, hold the potential to work as molecular switches which can regulate various useful functions.[1] Diarylethenes[2] are one of the most promising thermally irreversible photochromic families due to their remarkable fatigue resistance, enabling them to be used for molecular switches. However, structurally less versatile hexafluorocyclopentene is usually employed as the central ethene moiety so that modifications on the ethene moiety to append novel switchable functions in place of the hexafluoropropano-bridge have recently attracted much attention.[3–5] When a π-conjugating functional group is placed as the central ethene moiety and its property is altered by changing the π-conjugation, then a photo-triggered molecular switch can be constructed.[5] Among the chemical and physical properties that a molecule can switch, fluorescence is especially interesting and useful[6] since fluorescent molecules can be used as probes for intracellular processes[7] as well as for optical recording materials with fluorescence readout.[8] Moreover, in relation to the former use, biological fluorescence imaging techniques have been developed in order to visualize biological materials. For example, ultra high resolution imaging that we could hardly have previously imagined has recently been achieved.[9] To clarify the flow of materials in a living cell before and after an event such as stimuli applied to the cell, it is essential that the fluorescent ability of the probe is activated and that this should coincide with the stimulation at the same point where it is applied. It is also more useful if the fluorescence intensity is sensitive to the environment so that it works as a fluorescent probe when placed in a particular environment, *e.g.*, a light-switchable probe which works at a specific pH.[10]

It is clear that such a switchable fluorescence imaging system requires both high fluorescence quantum yield and high fluorescence switching efficiency. Although photochromic compounds exhibiting good reversibility in fluorescence intensity have been reported, most of them have relatively low fluorescence quantum yields and fluorescence switching efficiency.[7] It is also well documented that coumarin-type dyes possess excellent fluorescence quantum yields and that their fluorescence intensity is increased when an electron-donating group is substituted on C-7 of the coumarin framework.[11] Although a photochromic hexatriene structure possessing a coumarin as one of the terminal double bonds has been reported,[12] its fluorescence switching efficiency is not very impressive.

We report here on the synthesis, photochromism, and fluorescence switching of molecules having two thiazole rings and a coumarin skeleton as the central ethene moiety. Upon UV irradiation, we expected the fluorescence to be efficiently quenched by photocyclization due to the destruction of the coumarin structure. We have designed 3,4-bisthiazolylcoumarin **1*O***, its 7-methoxy derivative **2*O***, and 7-hydroxy derivative **3*O*** (Scheme 1). A stronger fluorescence of **2*O*** than that of **1*O*** could be expected due to the larger electron-donating ability of the 7-methoxy group. As for **3*O***, in addition to the photochromic interconversion, its fluorescence can be expected to become stronger by the generation of the phenolate anion upon base treatment[10,11c] so that it could be regarded as a dual-mode fluorescence switching molecule.

The synthetic key-step of **1*O***, **2*O*** and **3*O*** to introduce thiazole groups to the coumarin skeleton was performed by Suzuki–Miyaura coupling reactions of the corresponding coumarin, the 3- and 4-positions of which were substituted by a bromine and a trifluoromethanesulfonyloxy group, respectively.[13] The intermediate coumarins were synthesized according to previously reported procedures.[13a] Demethylation of **2*O*** by boron tribromide gave **3*O***. Characterizations of the novel compounds were carried out by ^{1}H NMR, FT-IR, UV-vis, and mass spectroscopy.

The photochromic reactions and fluorescent properties of **1**, **2** and **3** were investigated in various solvents with different polarities.[14] The conversion ratio to **2*C*** at the photostationary state (pss) upon 313 nm light irradiation in CH_2Cl_2 was



Scheme 1 Photochromism of the bisthiazolylcoumarin derivatives.

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determined by HPLC to be 98%. When the pss solution was irradiated with 578 nm light, the original absorption spectrum of the initial open form was restored, and HPLC analysis proved that all the closed form molecules were converted to the original open form again. As the conversion ratios of **1** and **2** were remarkably high (92–93% for **1**, 96–98% for **2**) in various solvents,[14] it has been proved that they are suitable for the switch.

As we expected, the fluorescence intensity of **1*O*** and **2*O*** decreased drastically by photochromic ring closure upon irradiation with 313 nm light due to the deformation of the coumarin structure. The fluorescence intensity was recovered upon successive irradiation with 578 nm light due to the restoration of the coumarin structure.[14] The fluorescence switching efficiency upon irradiation with 313 nm is excellent owing to the high conversion ratio. The fluorescence quantum yields of **1*O*** and **2*O*** excited with 330 nm light in hexane were 0.0025 and 0.0043, respectively. The larger quantum yield of **2*O*** over **1*O*** is attributed to the electron-donating ability of the methoxy group on C-7 of the coumarin structure.[11*b*]

With **2**, repetitive fluorescence switching was carried out by alternate irradiation with 313 and 578 nm light. Repetition of fluorescence switching could be successfully conducted without decrease in fluorescence intensity for five cycles.[14] However, the fluorescence quantum yields of both **1*O*** and **2*O*** were unsatisfactory. Therefore, we next examined the properties of **3*O*** which can be changed to phenolate by base treatment. As the electron-donating ability of phenolates is much stronger than that of the methoxy group, we expected the quantum yield of the fluorescence to increase.

Upon alternate irradiation with 313 and 578 nm light in dichloromethane and acetonitrile, **3** showed good photochromism. High conversion ratios to **3*C*** at the pss upon 313 nm light irradiation were also achieved at 98% and 95% for dichloromethane and acetonitrile, respectively. When 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was added to a dichloromethane solution of **3*O*** in order to generate the phenolate, a new absorption band centred at 404 nm appeared and reached saturation when 12.0 mole equivalents of DBU was added (Fig. 1a). The appearance of this new band is ascribable to the generation of a phenolate anion $\mathbf{3}\boldsymbol{O}_{\mathbf{anion}}$.[15] A reversible photochromic reaction between $\mathbf{3}\boldsymbol{O}_{\mathbf{anion}}$ and its pss ($\mathbf{3}\boldsymbol{C}_{\mathbf{anion}}/\mathbf{3}\boldsymbol{O}_{\mathbf{anion}} > 100$[16]) in dichloromethane was observed by means of alternate irradiation with 405 nm (Fig. 1b) and 578 nm light.

We then examined the light-triggered switching behavior of fluorescence for $\mathbf{3}_{\mathbf{anion}}$ in dichloromethane. The fluorescence switching of $\mathbf{3}\boldsymbol{O}_{\mathbf{anion}}$ upon alternate irradiation with 405 and 578 nm light was demonstrated as shown in Fig. 1c, and the fluorescence quantum yield of $\mathbf{3}\boldsymbol{O}_{\mathbf{anion}}$ in dichloromethane was determined to be 0.019. Although this value is more than four times as large as that of **2*O*** in hexane, it is still unsatisfactory for biological use. As these experiments were carried out in organic solvents, we then moved to solvents containing water as the major component in order to assess the applicability of **3** to biological systems.

To our great delight, the fluorescence of **3*O*** was strongly enhanced in water/methanol (2/1 v/v) with base treatment, as compared to that in organic solvents. Fig. 2 illustrates the change in the fluorescence spectra upon acid–base titrations using aqueous sodium hydroxide solution. The pK_a value of

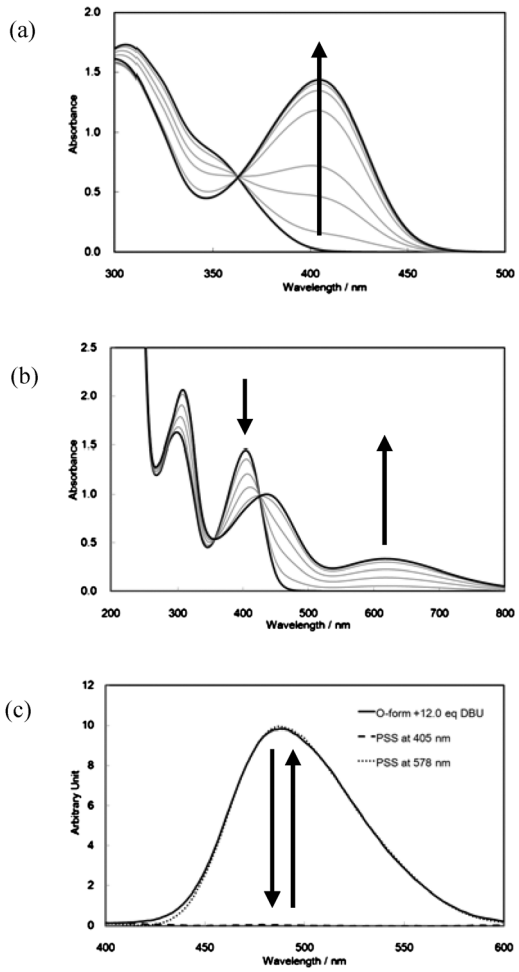

Fig. 1 (a) Change in absorption spectra of **3*O*** upon addition of DBU in CH_2Cl_2. Equivalence of DBU: 0 to 12. (b) Change in absorption spectra of $\mathbf{3}\boldsymbol{O}_{\mathbf{anion}}$ during irradiation with 405 nm light in the presence of 12.0 equiv. DBU in CH_2Cl_2. Irradiation time: 0–40 min. (c) Change in fluorescence spectra of $\mathbf{3}\boldsymbol{O}_{\mathbf{anion}}$ upon 405 and 578 nm light irradiation in the presence of excess DBU in CH_2Cl_2. excitation: 330 nm.

the phenol of **3*O*** was determined to be 6.84, which is consistent with that of 7-hydroxycoumarin.[11*a*] This pK_a value is suitable in controlling the changes between **3*O*** and $\mathbf{3}\boldsymbol{O}_{\mathbf{anion}}$ by the slight alteration of the pH in the biological systems. In fact, 14-fold increase was observed by changing the pH from 6.05 to 7.58. The fluorescence quantum yield of $\mathbf{3}\boldsymbol{O}_{\mathbf{anion}}$ with the excitation

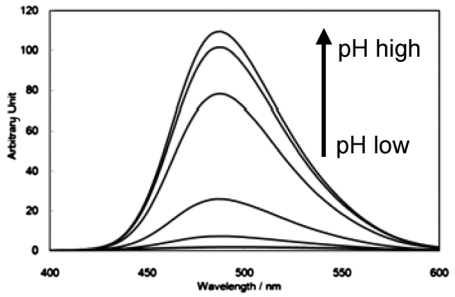

Fig. 2 Change in fluorescence spectra of **3*O*** with pH of the medium. Solvent: $CH_3OH/NaNO_3$ aqueous buffer solution = 1/2 (v/v), concentration: 5.1×10^{-6} mol dm^{-3}, excitation wavelength: 365 nm, pH of the solution: 2.64, 6.05, 6.38, 7.01, 7.58, 9.65.

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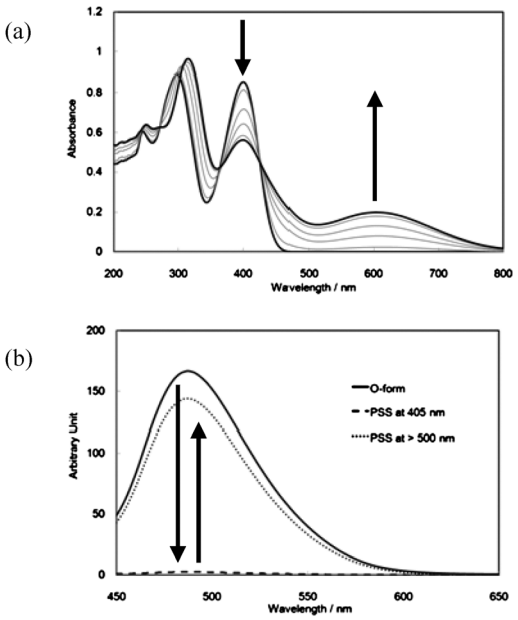

Fig. 3 (a) Change in absorption spectra of **3** during irradiation with 405 nm light in CH_3OH/10 mM sodium tetraborate buffer solution (pH = 9.48). Concentration: 4.38×10^{-5} mol dm^{-3}, light intensity: 0.25 mW cm^{-2}, irradiation time: 0–7 min. (b) Change in fluorescence spectra between $\mathbf{3}\boldsymbol{O}_{\mathbf{anion}}$ and $\mathbf{3}\boldsymbol{C}_{\mathbf{anion}}$ upon 405 and >500 nm light irradiation in CH_3OH/10 mM sodium tetraborate buffer solution (pH = 9.51). Concentration: 2.75×10^{-6} mol dm^{-3}, excitation wavelength: 420 nm.

wavelength of 330 nm at pH 9.48 was determined to be 0.25, which is satisfactorily large enough to apply to fluorescence imaging, even at more neutral conditions (Fig. 2).

In the mixed solvent of a buffer solution of sodium tetraborate and methanol (2/1 v/v, pH 9.48), **3** showed excellent photochromism upon alternate irradiation with 405 nm (Fig. 3a) and >500 nm light. The change in the fluorescence intensity of **3** was dramatic. When $\mathbf{3}\boldsymbol{O}_{\mathbf{anion}}$ at pH 9.48 was irradiated with 405 nm light and reaches its pss ($\mathbf{3}\boldsymbol{C}_{\mathbf{anion}}/\mathbf{3}\boldsymbol{O}_{\mathbf{anion}}$ = 98.5/1.5[16]), the intensity of the fluorescence excited at 420 nm decreased to 1.5% from the initial intensity before irradiation (Fig. 3b).

In conclusion, we have synthesized three novel 3,4-bisthiazolylcoumarins **1–3**. Among them, under the basic conditions, 7-hydroxy-3,4-bis(5-methyl-2-phenyl-4-thiazolyl)coumarin **3** changed its fluorescence intensity (quantum yield of 0.25 at pH 9.48 in buffered aqueous solution containing methanol) with photochromism as well as changes in the pH of the media. The intensity ratio of the photostationary state/open form at pH 9.48 was 1.5% while the intensity ratio of the open form at pH 7.58/pH 6.05 was 14-fold. These results show that the fluorescence intensity of $\mathbf{3}\boldsymbol{O}$ can be modulated by the photochromic reactions as well as by the pH of the media.

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