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Dual signaling of *m*-chloroperbenzoic acid by desulfurization of thiocoumarin

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ABSTRACT

The chemosignaling of widely used peracid oxidant of *m*-chloroperbenzoic acid (mCPBA) by the selective desulfurization of thiocoumarin was investigated. Thiocoumarin was efficiently converted into its corresponding coumarin by the reaction with mCPBA, and resulted in a pronounced fluorescent turn-on type signaling. The conversion also provided a significant change in absorption behavior which allowed a ratiometric analysis. The effective signaling could be used as a convenient determination method for mCPBA in aqueous environment.

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Selective detection or signaling of various oxidant species is important in chemical, biological, and industrial processes.[1] Recently, considerable research effort has been devoted to the signaling and visualization of biologically important reactive oxygen species, such as hydrogen peroxide,[2] hypochlorous acid,[3] peroxynitrite,[4] and nitric oxide.[5] However, convenient signaling systems for peracid oxidants are scarce, though they are used widely in synthetic organic chemistry.

m-Chloroperbenzoic acid (mCPBA) is a peroxycarboxylic acid used widely as an oxidant in organic synthesis due to its versatile oxidizing power and relative ease of handling. Its main areas of use are the conversion of ketones to esters (Baeyer–Villiger oxidation),[6] the epoxidation of alkenes,[7] the oxidation of sulfides to sulfoxides and sulfones,[8] and the oxidation of amines to amine oxides.[9] In many reactions, mCPBA is highly reactive and more selective than hydrogen peroxide or other peracids. In some applications, exact amount of oxidant should be used to avoid side reactions; for example, oxidation of sulfide with mCPBA resulted in sulfoxide and sulfone depending upon the amounts of mCPBA used.[7] mCPBA could be determined using iodometric titration with iodide[10] and via GC using the conversion of methyl phenyl sulfoxide into its sulfone.[11] mCPBA can also be determined by spectroscopic methods, such as oxidation of azo dye[12] and enhanced chemiluminescence for the oxidation of luminol.[13] However, simple and convenient spectroscopic methods to determine mCPBA concentrations are rare.

Thioamides are readily transformed to their corresponding amides via reaction with mCPBA under mild conditions.[14] We developed a new chromogenic and fluorogenic signaling system for mCPBA based on the desulfurization of thiocoumarin. In the presence of mCPBA, the sulfur atom of thiocoumarin was expelled by converting into its oxo analog. This change resulted in a large fluorescence enhancement and ratiometrically analyzable absorption changes.

Treatment of 7-ethoxycoumarin **2** with Lawesson's reagent yielded desired thiocoumarin **1** (Scheme 1). A more chromogenic thiocoumarin derivative **4** was also prepared from coumarin 6 **3**.[15] In 90% aqueous acetonitrile, compounds **1** and **4** appeared yellow and red, respectively, with relatively weak emissions due to the thiocarbonyl function of thiocoumarins.

First, we assayed the chemical resistivity of 7-ethoxycoumarin **2**, which is the expected product of mCPBA signaling by the desulfurization of thiocoumarin **1**, toward the mCPBA oxidant. Upon treatment of ethoxycoumarin **2** with 100 equiv of mCPBA in aqueous acetonitrile, the absorption and fluorescence characteristics were not affected (Figs. S1 and S2, Supplementary data). The ^{1}H NMR spectrum of **2** in the presence of 2 equiv of mCPBA in deuterated acetonitrile did not change either (Fig. S3, Supplementary data). These observations suggest that 7-ethoxycoumarin has chemical resistance to oxidative stress from mCPBA. An attempt to design more chromogenic system **4**, based on coumarin 6 with a 3-benzothiazolyl substituent, was unsuccessful due to the insufficient stability of **3** itself toward mCPBA.

Thiocoumarin **1** exhibited a very weak emission around 394 nm in 90% aqueous acetonitrile solution. Upon treatment with increasing amount of mCPBA, a steady fluorescence enhancement at 394 nm was observed (Fig. 1). The enhancement was over 120-fold and the solution changed from dark to blue under UV-illumination. The fluorescence behavior of **1** did not vary significantly in acetate, phosphate, or tris buffered solutions at pH 4.8, 7.0, and 8.1, respectively (Fig. S4, Supplementary data). To prevent mCPBA from possible reaction with amines in the buffer,[16] signaling experiments were carried out in phosphate buffered 90% aqueous acetonitrile (H_2O/CH_3CN = 90:10, v/v) at pH 7.0. Using a 90% aqueous acetonitrile solution for the signaling of mCPBA is because the signaling is more efficient in aqueous solutions having higher water content (Fig. S5, Supplementary data).

To check the possibility of chromogenic signaling of **1**, UV–vis titration with mCPBA was carried out in 90% aqueous acetonitrile. Upon titration with mCPBA, the strong absorption band of **1** at

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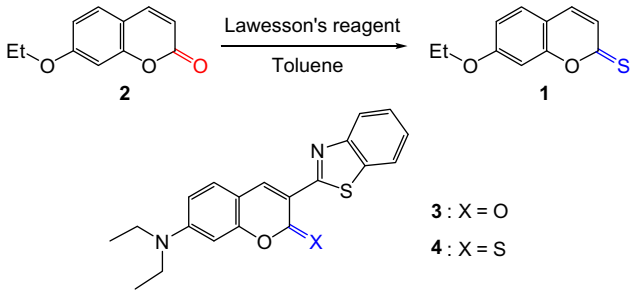


Scheme 1. Preparation of thiocoumarins.

406 nm steadily decreased, and a new band at 324 nm increased (Fig. 2). Concomitantly, solution color changed from yellow to colorless. Isosbestic point was not so well-defined early in the titration, which might be due to the formation of thermally unstable sulfine intermediate.[17] However, plotting the absorbance changes as a function of mCPBA at 406 and 324 nm showed well-defined profiles (inset of Fig. 2). Particularly, absorbance changes in response to the variation of mCPBA could also be analyzed by ratiometry using the ratio of the absorbances at 324 and 406 nm (Fig. S6, Supplementary data).

Effective chromogenic and fluorogenic signaling behavior of **1** is due to mCPBA promoted desulfurization of thiocoumarin to coumarin (Scheme 2). The conversion from **1** to **2** was confirmed by NMR, UV–vis, and fluorescence measurements. The ^{1}H NMR spectrum of **1** in the presence of 2 equiv of mCPBA in CD_3CN/D_2O (1:1, v/v) was almost identical to that of **2** (Fig. 3). The UV–vis and fluorescence spectra of **1** in the presence of 100 equiv of mCPBA were also identical to both of **2** in the absence and presence of same amount of mCPBA.[18] Conversion was also confirmed by measurement of ^{1}H NMR spectrum of the purified reaction product of **1** with mCPBA, which is identical to that of **2**, in acetonitrile.

mCPBA signaling by **1** was completed within 5 min (Fig. S7, Supplementary data). Under the same conditions, thiocoumarin **1** was stable and did not hydrolyze appreciably even after 24 h of sample preparation. The detection limit[19] of **1** for mCPBA was 5.1 μM in 90% aqueous acetonitrile solution.[20] To check the practical applicability of **1**, possible interferences from common metal ions were measured ([**1**] = 5.0×10^{-6} M, [mCPBA] = 2.5×10^{-4} M, [M^{n+}] = 5.0×10^{-4} M). In fact, thiocoumarin derivative was used as a signaling tool for Hg^{2+} ions by a similar desulfurization process. [21] Although, Co^{2+} and Hg^{2+} caused significant interference,

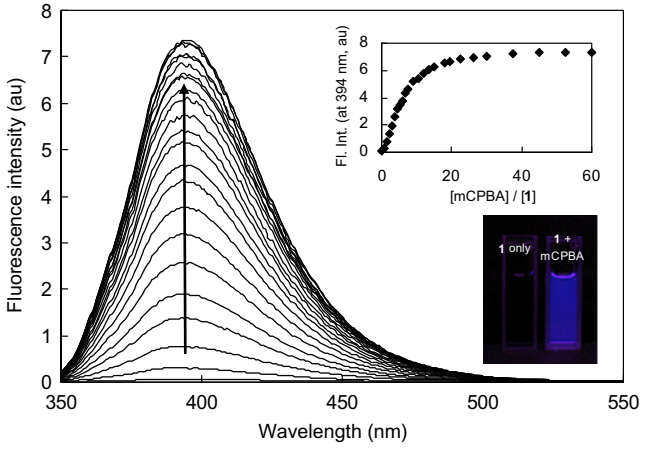


Figure 1. Fluorescence titration of **1** with mCPBA. In 90% aqueous acetonitrile at pH 7.0 (10 mM phosphate buffer). [**1**] = 5.0×10^{-6} M. λ_{ex} = 340 nm.

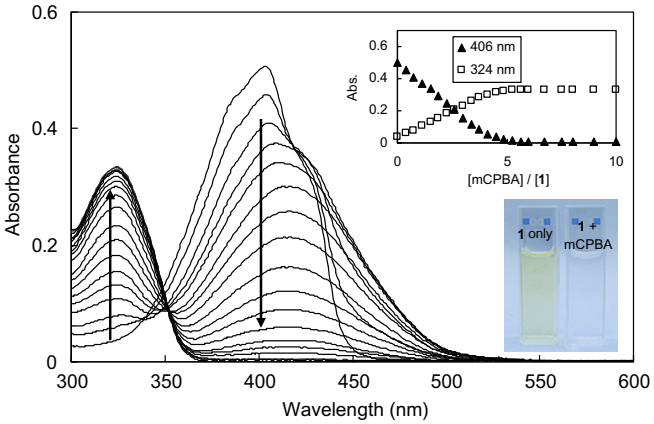
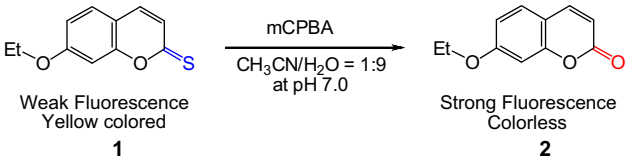


Figure 2. UV–vis titration of **1** with mCPBA. In 90% aqueous acetonitrile at pH 7.0 (10 mM phosphate buffer). [**1**] = 2.0×10^{-5} M.



Scheme 2. Signaling of mCPBA by thiocoumarin **1**.

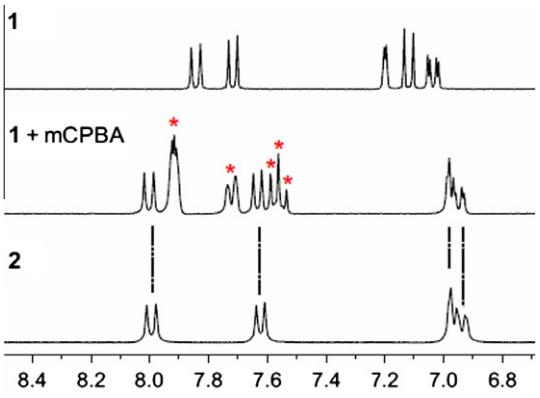


Figure 3. Partial ^{1}H NMR spectra of **1**, **1** + mCPBA, and **2**. In CD_3CN/D_2O (1:1, v/v). [**1**] = [**2**] = 5.0×10^{-3} M. [mCPBA] = 1.0×10^{-2} M. Red starred peaks are residual mCPBA resonances.

common coexisting metal ions of alkali (Na^+, K^+), alkaline earth (Mg^{2+}, Ca^{2+}), and transition metal ions (Fe^{3+}, Ni^{2+}, Cu^{2+}, Zn^{2+} and Cd^{2+}) did not affect the signaling of mCPBA. The reason for these substantial interferences from Co^{2+} ($I_{mCPBA+Co(II)}/I_{mCPBA}$ = 0.65) and Hg^{2+} ($I_{mCPBA+Hg(II)}/I_{mCPBA}$ = 0.22) might be due to the undesirable reaction of mCPBA itself with these transition metal ions, as has been reported for Co^{2+} ions.[22]

Finally, the ability to discriminate mCPBA from other widely used oxidants, hydrogen peroxide, *tert*-butyl hydroperoxide (TBHP), and peracetic acid (PAA), was tested (Fig. 4).[10,11] Compound **1** exhibited a much larger response (~80-fold) toward mCPBA than hydrogen peroxide, as reported for the reaction with azo dyes[12] and TBHP. On the other hand, another important peracid, PAA, responded considerably with an 11-fold increase in fluorescence intensity. This observation suggests that thiocoumarin **1** can selectively signal mCPBA in the presence of a large excess of hydrogen peroxide or TBHP.

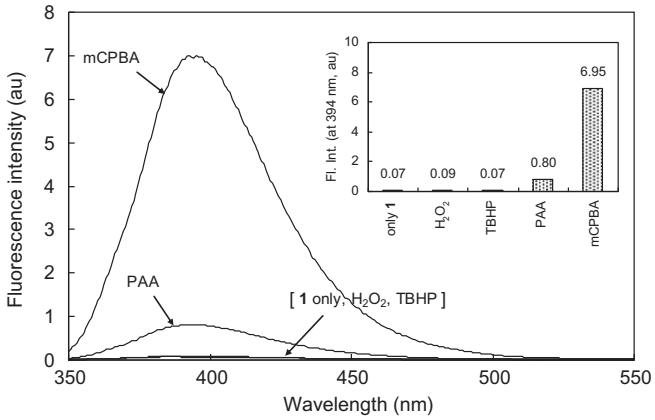


Figure 4. Changes in fluorescence spectra of **1** in the presence of commonly used oxidants. [**1**] = 5.0×10^{-6} M, [mCPBA] = [H_2O_2] = [TBHP] = [PAA] = 5.0×10^{-4} M. λ_{ex} = 340 nm.

In summary, a convenient dual signaling system for mCPBA was devised based on a simple thiocoumarin derivative. Signaling was due to the efficient desulfurization of thiocoumarin to coumarin by mCPBA. Thiocoumarin also exhibited mCPBA-selective signaling in the presence of a large excess of hydrogen peroxide. The reported system could be used as a convenient spectroscopic signaling tool to determine mCPBA concentration.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.066.

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18. *Compound* **1**: λ_{max} = 406 nm, $\varepsilon = 2.52 \times 10^4$ M^{-1} cm^{-1}. Φ = 0.050. Compound **2**: λ_{max} = 324 nm, $\varepsilon = 1.65 \times 10^4$ M^{-1} cm^{-1}. Φ = 0.0004 in 90% aqueous acetonitrile at pH 7.0. Quantum yields were measured using anthracene as a quantum yield standard (Φ = 0.27 in ethanol).
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