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# Signaling of chloramine: a fluorescent probe for trichloroisocyanuric acid based on deoximation of a coumarin oxime



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## ABSTRACT

A new chloramine signaling probe, based on a coumarin oxime, was developed. The coumarin oxime **1** exhibited efficient off–on type fluorescent signaling behavior toward trichloroisocyanuric acid (TCCA) in an aqueous acetonitrile solution. The signaling is due to the TCCA-assisted transformation of the oxime function to its carbonyl analogue. The presence of common metal ions and anions did not interfere with the TCCA signaling of this probe. Probe **1** was found to be useful for the sensitive determination of the concentration of the practical oxidant TCCA in an aqueous environment, with a detection limit of  $7.58 \times 10^{-7}$  M.

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Chloramines are inorganic or organic nitrogen compounds, which contain one or more chlorine atoms attached to the nitrogen atoms. They are inexpensive, stable in aqueous solution, and environmentally benign oxidants that are broadly used both in daily life and for industrial applications.<sup>1</sup> Because they are easier to handle than chlorine gas or metal hypochlorites, they are widely used in the purification of drinking water and as sanitizing agents in swimming pools.<sup>2</sup> Chloramines are also commonly used in synthetic reactions.<sup>3,4</sup> The usefulness of chloramines arises from the fact that they behave as a source of both a halonium ion and various nitrogen-containing species.<sup>5</sup> As a result, these reagents can react with a wide range of functional groups, leading to a number of molecular transformations such as chlorination of alkenes and aromatics, oxidation of ethers and alcohols, epoxidation of alkenes, and nitrosation of amines.<sup>6</sup> In organic syntheses, hypochlorites could also be substituted with *N*-chloramines, especially when anhydrous conditions are necessary. Among the organic chloramines, in particular, trichloroisocyanuric acid (TCCA) and sodium N-chloro-p-toluenesulfonamide (chloramine-T) have become increasingly important.

Chloramines have commonly been analyzed by titrimetry using iodide, amperometry, and flow-injection analysis.<sup>7</sup> Specific analytical methods such as HPLC, GC, and mass spectrometry have also been used for these oxidants.<sup>8</sup> The colorimetric method using

*N*,*N*-diethyl-*p*-phenylenediamine (DPD) is one of the more commonly used techniques for the analysis of chlorine in water.<sup>9</sup> However, we could not find any literature on the use of fluorescent signaling approach for analyzing chloramines.

Reaction-based probes have attracted much research interest recently due to their specificity and cumulative signaling advantages.<sup>10</sup> In particular, there are noticeable achievements in the signaling or visualizing of biologically important reactive oxygen or nitrogen species, such as hydrogen peroxide, peroxynitrite, and hypochlorous acid.<sup>11</sup> However, optical probes for practical oxidants such as peracids and chloramines are not reported often in spite of their importance in a variety of industrial applications. We have developed a series of reaction-based optical probes for the determination of these practical oxidants, using desulfurization of thioamides for peracetic acid and oxone, thiocoumarin for mCPBA, as well as oxidative hydrolysis of phenolic acetate for perborates.<sup>12</sup>

Protection of carbonyl functions by converting them to oximes is one of the most useful tactics in organic synthesis.<sup>13</sup> In this case, deprotection of oximes to form carbonyls could be effected by a variety of oxidation and reduction reactions.<sup>14</sup> Recently, a broad range of *N*-halosulfonamides has been reported for the regeneration of carbonyl compounds from oximes (Scheme 1).<sup>15</sup> We devised a new reaction-based probe for the convenient determination of practical oxidant chloramines by using the oxime-carbonyl transformation. The oxime derivative of ethoxycoumarin exhibited a pronouncedly sensitive fluorogenic signaling behavior toward the industrially important chloramine TCCA in aqueous acetonitrile solution.





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**Scheme 1.** Deprotection of oximes with *N*-halosulfonamides.

Probe **1** for chloramine signaling was prepared by a two-step reaction from 7-ethoxycoumarin (Scheme 2). Thionation of 7-ethoxycoumarin with Lawesson's reagent yielded thiocoumarin **2** (toluene, 65%).<sup>12c</sup> Reaction of thiocoumarin **2** with hydroxylamine produced the desired 7-ethoxycoumarin oxime **1** (NH<sub>2</sub>OH, EtOH, 80%).<sup>16</sup> We tried to prepare more chromogenic coumarin derivatives having dialkylamino (coumarin 334) or benzothiazole substituents (coumarin 6), but the stability of the parent dyes under the oxidative stress of the chloramine under consideration here was inadequate.

Probe **1** exhibited an absorption band at 325 nm in 90% aqueous acetonitrile solution, phosphate buffered at pH 8.0, which is similar to that of 7-ethoxycoumarin ( $\lambda_{max}$  = 323 nm). On the other hand, probe **1** showed weak fluorescence due to the quenching effect of the oxime group under the same conditions.<sup>17</sup> We surveyed the preliminary fluorescent signaling behavior of probe 1 toward a series of practical oxidants, such as hydrogen peroxide, *tert*-butyl hydrogen peroxide (TBHP), perborate, peracetic acid (PAA), and the chloramine TCCA (Fig. 1 and Fig. S1, Supplementary data). Among the tested oxidants, only TCCA and HOCl showed prominent signaling under the measurement conditions. The fluorescence enhancements  $I/I_0$  observed at 392 nm were 105-fold for TCCA and 102-fold for HOCl. The colorimetric or fluorescent signaling of HOCl, due to the deoximation of oxime derivatives of various substances (such as BODIPY and phenanthroimidazole dye) to their carbonyl groups, have already been reported.<sup>18</sup> Peracetic acid also showed a considerable response ( $I/I_0 = 11.8$ ). Other commonly used oxidants, such as hydrogen peroxide, TBHP, perborate, percarbonate, and superoxide, showed negligible signaling: the ratio  $I/I_0$ varied between 0.79 for TBHP and 1.69 for perborate. The significant response toward HOCl in the selective TCCA signaling by 1 might not be a practical problem, because TCCA is generally used as a single component oxidant in many applications. We tried to obtain a signaling condition that could differentiate TCCA from HOCl, but failed. That can be ascribed to the fact that the TCCA in aqueous solution in situ generates HOCl as an active oxidant.<sup>19</sup> Meanwhile, the UV-vis absorption behavior of compound **1** was not useful for the determination of TCCA. because TCCA did not induce any diagnostic changes in the spectral properties of **1** (Fig. S2, Supplementary data).

The signaling is due to the oxidative transformation of the oxime moiety of **1** to a coumarin carbonyl function (Scheme 3).<sup>20</sup> The <sup>1</sup>H NMR spectrum of the purified reaction product, obtained by treatment of **1** with TCCA, was identical to those of ethoxy-coumarin (Fig. 2). In the <sup>1</sup>H NMR spectrum, the resonances for







**Figure 1.** Fluorescence spectra of **1** in the presence of practical oxidants. Inset: fluorescence image of **1** in the absence and presence of TCCA. The spectra were recorded in a mixture of CH<sub>3</sub>CN and phosphate buffer solution (pH 8.0, 10 mM), (1:9, v/v). **[1]** =  $5.0 \times 10^{-6}$  M, [oxidant] =  $5.0 \times 10^{-5}$  M.  $\lambda_{ex}$  = 325 nm. PAA: peracetic acid, TBHP: *tert*-butyl hydrogen peroxide.





**Figure 2.** Partial <sup>1</sup>H NMR spectra of **1** in the absence and presence of TCCA, and 7-ethoxycoumarin. [**1**] = [7-ethoxycoumarin] = 15 mM and [TCCA] = 6 mM in CDCl<sub>3</sub>. Middle spectrum (**1** + TCCA) was obtained after purification by column chromatography.



**Figure 3.** Fluorescence intensity ratio  $I/I_0$  at 392 nm of **1** + TCCA and **1** in the presence of various metal ions. [**1**] =  $5.0 \times 10^{-6}$  M, [TCCA] = [ $M^{n+}$ ] =  $5.0 \times 10^{-5}$  M. In a mixture of CH<sub>3</sub>CN and phosphate buffer solution (pH 8.0, 10 mM), (1:9, v/v).  $\lambda_{ex}$  = 325 nm.



**Figure 4.** Changes in the fluorescence intensity ratio of **1**-TCCA system at 392 nm in the presence of metal ions as background. [**1**] =  $5.0 \times 10^{-6}$  M, [TCCA] = [M<sup>n+</sup>] =  $5.0 \times 10^{-5}$  M. In a mixture of CH<sub>3</sub>CN and phosphate buffer solution (pH 8.0, 10 mM), (1:9, v/v).  $\lambda_{ex}$  = 325 nm.



**Figure 5.** Fluorescence titration of **1** with TCCA. Inset shows the changes in fluorescence intensity at 392 nm of **1** as a function of TCCA. [**1**] =  $5.0 \times 10^{-6}$  M, [TCCA] = from 0 to  $4.0 \times 10^{-6}$  M. In 90% aqueous acetonitrile (pH 8.0 phosphate buffer, 10 mM).  $\lambda_{ex}$  = 325 nm.

the 3-H and 4-H protons that are adjacent to the oxime function of 1 (7.10 and 6.84 ppm) were shifted significantly downfield (7.63 and 7.36 ppm). The transformation of the oxime of 1 to its carbonyl form was also confirmed by <sup>13</sup>C NMR spectroscopy (Fig. S3, Supplementary data).

The coumarin oxime **1** showed TCCA-selective signaling behavior in the presence of common metal ions. For the alkali, alkaline earth, and representative transition metal ions that were studied, the fluorescence intensity ratio  $I/I_0$  at 392 nm varied in a narrow range between 0.93 for Mg<sup>2+</sup> and 1.44 for Ag<sup>+</sup> ions (Fig. 3). Oxime **1** also showed negligible responses toward commonly encountered anions. The ratio  $I/I_0$  fluctuated in a limited range between 1.02 for F<sup>-</sup> and 4.43 for HCO<sub>3</sub><sup>-</sup> anions (Fig. S4, Supplementary data).

To obtain an insight into the practical applicability of this method, the selective signaling of 1 for TCCA was tested under competitive conditions. In the presence of commonly encountered metal ions or anions as background species, the TCCA-selective signaling of 1 was found not to be significantly affected (Fig. 4 for metal ions and Fig. S5, Supplementary data, for anions). This observation implies that the coumarin oxime 1 could be used as a TCCA-selective fluorescent probe in the presence of commonly encountered metal ions and anions in environmental samples. The stability of the probe was satisfactory between pH 3 and 10, and the fluorescence was not affected by pH changes. However, the TCCA signaling increased as the pH of the solution increased, but was not significantly changed in alkaline media at pH 8-10 (Fig. S6, Supplementary data). In addition, the TCCA signaling by **1** was fast and completed within 1 min after sample preparation (Fig. S7, Supplementary data).

The quantitative signaling behavior of **1** was studied by fluorescence titration with TCCA (Fig. 5). As the concentration of TCCA increased, the emission intensity at 392 nm increased steadily, as shown in the inset of Figure 5. Plotting of the fluorescence intensity at 392 nm, as a function of TCCA concentration, showed a useful calibration plot up to  $3.0 \times 10^{-6}$  M. From the concentration-dependent signaling behavior, the detection limit of **1** for the determination of TCCA, in 90% aqueous acetonitrile, was estimated to be  $7.58 \times 10^{-7}$  M.<sup>21</sup>

Finally, application of the probe **1** as a practically useful test strip was attempted (Fig. 6).<sup>22</sup> Probe **1** in acetonitrile solution (5 mM) was applied on a TLC plate (Silica gel). Addition of TCCA solution of varying concentrations on the plate resulted in the enhancements of blue fluorescence. The obtained intensity profile implies that the probe could readily signal TCCA down to  $10^{-5}$  M range without any sophisticated instruments.

In summary, a new trichloroisocyanuric acid (TCCA)-selective probe, based on the coumarin oxime, was developed. The oxime derivative of ethoxycoumarin showed prominent fluorescence-on type signaling behavior toward industrially important chloramine TCCA, due to the oxime-carbonyl transformation. The selective signaling was also achieved in the presence of common metal ions and anions as background species. In addition, the TCCA-selective signaling was possible in the presence of other commonly used practical oxidants such as peracids and peroxides.

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#### Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.10. 132. These data include MOL files and InChiKeys of the most important compounds described in this article.



Figure 6. Pictures of changes in (a) fluorescence and (b) blue channel intensities of 1 in the presence of varying amounts of TCCA under a UV lamp.<sup>23</sup> Intensities of blue channel were obtained by recording blue channel values (0–255) of image in Adobe Photoshop. [TCCA] = from 0 to  $1.0 \times 10^{-4}$  M in acetonitrile solution.

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- 20. Independent reaction of 1 with TCCA under the signaling conditions yielded 65% of 7-ethoxycoumarin and unidentified side-products. The reaction product was purified by the column chromatography (silica gel, dichloromethane/ methanol = 19:1, v/v).
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- 22. TLC plate (Silica 60 F254, Merk KGaA) was soaked in the probe solution (5 mM, in acetonitrile) and allowed to dry in ambient atmosphere. For detection of TCCA, prepared TLC plate was dipped into TCCA solution (in acetonitrile) of varying concentrations for 5 s. After dry in air, fluorescence changes in the TLC plate were monitored under a UV lamp.
- 23. Optical images were obtained using a camera of iPhone 5S (Apple. Inc). The picture was analyzed with blue channel values of image in Photoshop CS6 (Adobe Systems Incorporated).