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ORIGINAL PAPER

Selective and Sensitive Fluorescence Chemosensor for the Hypochlorite Anion in Water

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Abstract Based on an oxidized irreversible ring-opening process of the spirolactam of rhodamine 6G to turn on the fluorescence pathway, a highly sensitive, selective fluorescent and easy accessible chemosensor for ClO^- has been reported. Upon reaction of the chemosensor with ClO^- ions, a fluorescent enhancement factor over 60-fold is observed. The chemosensor shows a remarkably high selectivity to discriminate between ClO^- and other ROS, such as H_2O_2, TBHP etc., and a wide range of the environmentally and biologically relevant anions and metal ions. The oxidized irreversible ring-opening process of the chemosensor also triggers a visible colorimetric change from colorless to pink, leading to production of both "naked-eye" and fluorimetric detection of ClO^- anion. The detection limit is estimated to be 2×10^{-8} M based on a signal-to-noise ratio of 3:1 method. The chemosensor can be used within a pH span of 6–11.5. The chemosensor also shows excellent performance in natural water samples.

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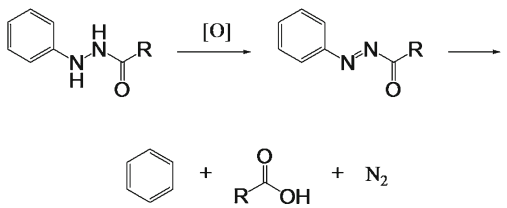
Introduction

Reactive oxygen and nitrogen species (ROS/RNS) formed during the metabolism of oxygen in living systems are known to be essential to several biological functions [1, 2] which are also believed to be implicated in aging processes and numerous diseases such as atherosclerosis and cancer [3–5]. As one of the biologically important ROS, hypochlorous acid (HOCl) is weakly acidic and partially dissociates into the hypochlorite ion (OCl^-) in the physiological pH solutions [6]. Endogenous HOCl and OCl^-, nonspecific oxidizing and chlorinating agents, are essential to life and have important antibacterial properties which are believed to be produced in vivo by hydrogen peroxide and chloride ions in activated neutrophils catalyzed by a heme-containing enzyme myeloperoxidase (MPO) [7–10]. However, excess levels of HOCl and OCl^- can lead to serious damage to several biomolecules [11–14], cell structures or tissue [5–16], causing many diseases, such as cardiovascular diseases, neuron degeneration, atherosclerosis, arthritis, and cancers [17–22]. Nevertheless, the detailed pathogenic mechanism is not fully understood, because of the lack of a feasible method for detecting HOCl and its anion. On the other hand, hypochlorite (ClO^-) is widely used in our daily life, such as disinfection of drinking water, household bleach agent, etc. Typically, it is used in the concentration range of 10^{-5}–10^{-2} M [23]. Such highly concentrated hypochlorite solutions are a potential health hazard to human and animals [24]. Thus, the development of highly sensitive

and selective methods for the determination of trace amounts of HOCl and its anion in various media are of considerable importance for the environment and human health.

In recent years, a number of analytical methods, such as colorimetric, luminescent, electrochemical and chromatographic methods [25–33], have been proposed for the detection of ClO^-, among which fluorescent probes play an important role in this respect due to their great temporal and spatial resolution capability as well as high sensitivity [34–36]. However, only a limited number of fluorescent chemosensors have been made available for OCl^- detection to date and in particular for OCl^--specific determination [37, 38]. Indeed, most of the reported fluorescent chemosensors for OCl^- detection are reaction-type by taking advantage of the high oxidization property of this anion. The caged fluorescent signal of the chemosensor were first oxidized by OCl^-, and then decomposed to a fluorescent product and resulted in the fluorescent signal 'turn on'. For instance, dihydrofluorescein and dihydrorhodamine derivatives have been suggested as chemosensors for OCl^- detection, but their fluorescence responses lack selectivity because of the cross-reactions with other ROS [37–39]. Ma and co-workers [29] reported a rhodamine 6G chemosensor with good selectivity for OCl^-, but its working media is in strong basic condition. Nagano and co-workers [37, 38] reported a fluorescence probe with good selectivity for hypochlorous acid, but its synthetic route was rather complicated. Obviously, the very reliable fluorescence chemosensors for HOCl and OCl^- with highly sensitive and selective are still required arises from its biological functions and/or deleterious effects for human and the environment [40, 41].

It is known that phenylhydrazido group has been widely used as an important protection group for the carbonyl of amino acids in peptide synthesis. It can be removed easily by oxidization into N-acyl-α-amino acid phenyldiimides with oxide reagents, such as NBS etc., which subsequently undergoes decomposition in the presence of nucleophilic reagents or water (Scheme 1) [42]. Since hypochlorite is a strong oxidant, it is reasonable to believe that the reaction should be initiated by OCl^-. In this paper, we reported a new OCl^- specific fluorescence chemosensor based on the known compound rhodamine 6G hydrazide (R6GH) (Inset of Fig. 3), which was synthesized in one step by the reaction of rhodamine 6G with hydrazine [43]. R6GH shows excellent selectivity and sensitivity for OCl^- over relevant competing reactive oxygen species (ROS) and metal ions with a fluorescent enhancement factor over 60-fold by a oxidization ring-opening process of spirolactam of rhodamine 6G to turn on the fluorescence pathway, thus resulting in the large enhancement of fluorescent intensity in water solution. R6GH also shows good performance in natural water samples.



Scheme 1 Oxidization and decomposition procedures of N-acetyl-α-amino acid phenylhydrazides

Experimental

All cations in the form of nitrate salts, all anions in the form of sodium salts, H_2O_2 and *tert*-butylhydrogen peroxide (TBHP) were purchased from Sigma–Aldrich Chemical Company and used without further purification. All other chemicals used were local products of analytical grade. All solvents used in spectroscopic test are spectroscopic grade. R6GH was synthesized according to the literature [43]. UV absorption spectra were recorded on a UV-2550 UV–VIS spectrophotometer (Shimadzu, Japan). Fluorescence measurements were performed using an F-4600 fluorescence spectrophotometer (Hitachi, Japan) equipped with a plotter unit and a quartz cell (1 cm × 1 cm).

Results and Discussion

Firstly, we evaluated the response of R6GH to a wide range of the environmentally and biologically relevant anions, metal ions and reactive oxygen species H_2O_2 and *tert*-butylhydrogen peroxide (TBHP) by absorption and emission spectrum. The UV–vis spectra of R6GH (50 μM) in water exhibited only a very weak band above 500 nm, which was

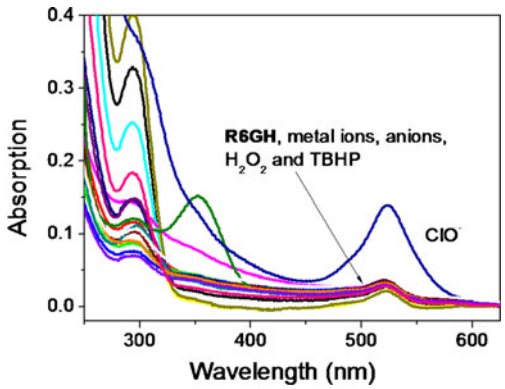


Fig. 1 Absorption spectra of R6GH (50 μM) with addition of sodium salts of Cl^-, ClO_4^-, H_2O_2, NO_2^-, NO_3^- and SO_4^{2-} (100 equiv.), ClO^- (3.0 equiv.), nitrate salts of Ca^{2+}, K^+, Mg^{2+}, Pb^{2+}, Ni^{2+}, Zn^{2+} and H_2O_2 (10 equiv.), nitrate salts of Fe^{3+}, Cu^{2+}, Hg^{2+} and TBHP (1.0 equiv.) in H_2O at pH 7.0

Fig. 2 Photograph of 50 μM R6GH in the presence of different of the nitrate salts (10.0 equiv) of ClO_4^-, H_2O_2, NO_2^-, ClO^-, TBHP, Cu^{2+} and Hg^{2+} in H_2O

assigned to a trace amount of the ring-opened form of R6GH. Upon the addition of 4 equivalents of ClO^-, the absorbance was significantly enhanced with a new peak appearing at 524 nm (Fig. 1), suggesting the interaction of R6GH with ClO^- caused the ring-opened form of R6GH. Meanwhile, the characteristic color change from colorless to pink indicates that R6GH can serve as a "naked-eye" indicator for the ClO^- anion (Fig. 2). As shown in Fig. 3, the fluorescence spectra of R6GH (5 μM) exhibits a very weak fluorescence at 548 nm corresponding to a trace amount of the ring-opened form of R6GH, which is consistent with that of UV/vis spectra. The addition of 4 equivalents of ClO^- ion results in an obviously enhancement of the emission intensity (with an enhancement factor over 60-fold) positioned at 548 nm (OFF-ON). However, the addition of Cl^-, ClO_4^-, H_2O_2, NO_2^-, NO_3^- and SO_4^{2-} (100 equiv), nitrate salts of Ca^{2+}, K^+, Mg^{2+}, Pb^{2+}, Ni^{2+}, Zn^{2+}, Fe^{3+} (10 equiv), nitrate salts of Cu^{2+} and Hg^{2+} (1.0 equiv) has no obvious effect on the fluorescence emission. But the addition of higher concentration of Cu^{2+} and Hg^{2+} (10 equiv) produce a slight enhancement of the emission intensity (with an enhancement factor of 8-fold for Hg^{2+} and 3-fold for Cu^{2+}) (Fig. S1, ESI), which is similar to a reported results of rhodamine B hydrazide (RBH) [44]. On the other hand, even though Sasamoto and coworkers [45] reported that RBH can reacted with NO_2^- at pH 3.0 at 60 °C, no reaction between

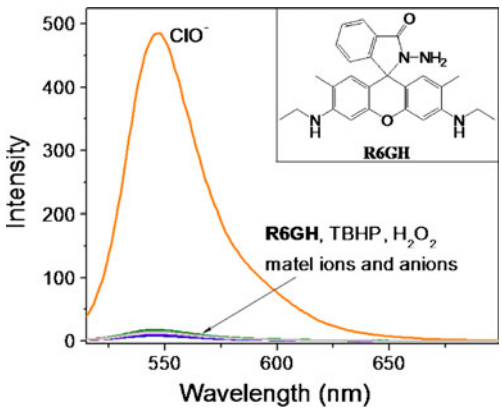


Fig. 3 Fluorescence spectra of R6GH (5 μM) with the addition of the sodium salts of Cl^-, ClO_4^-, H_2O_2, NO_2^-, NO_3^-, SO_4^{2-} (100 equiv) and ClO^- (4 equiv), the nitrate salts of Ca^{2+}, K^+, Mg^{2+}, Pb^{2+}, Ni^{2+}, Zn^{2+}(10 equiv), Fe^{3+}, Cu^{2+}, Hg^{2+} (1.0 equiv), TBHP and H_2O_2 (10 equiv) in H_2O at pH 7.0. Inset: chemical structure of R6GH

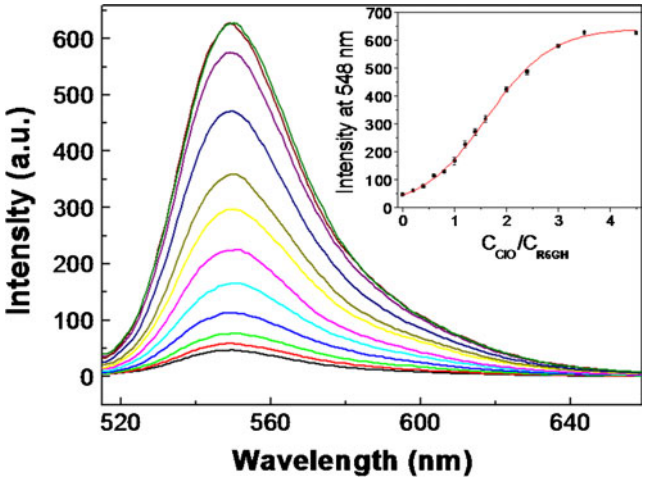


Fig. 4 Fluorescence spectra of R6GH (5 μM) with the addition of various concentrations of NaClO in H_2O at pH 7.0 with an excitation at 505 nm. C_{ClO^-}/C_{R6GH}: 0, 0.2, 0.6, 0.8, 1.2, 1.4, 1.8, 2.0, 2.6, 3.0, 4.0 respectively. Inset: Plot of the values of I_F at 548 nm with respect to the added NaClO concentrations (C_{ClO^-}/C_{R6GH}) (0–4.0 equiv)

R6GH and NO_2^- was detected in water at pH 7.0, suggesting that R6GH is resistant to in situ produced NO under physiology condition. R6GH is also resistant to H_2O_2 (10 equiv) and *tert*-butylhydrogen peroxide (TBHP, 1 equiv) in water, which is similar to RBH under physiology conditions [46]. At the same time, hydroxyl radical ($^{\bullet}OH$) is one the most important ROS in biologic systems. The response of R6GH to different concentrations of $^{\bullet}OH$ were also evaluated under the same condition (Fig. S2, ESI). No obvious enhancement of the emission intensity even at high concentration (50.0 equivalents) indicated that $^{\bullet}OH$ didn't interfere with ClO^- analysis. It is note that the selectivity of R6GH for ClO^- over H_2O_2, NO and $^{\bullet}OH$ is particularly important because H_2O_2, NO and $^{\bullet}OH$ are the most important ROS species in vivo [45] and frequently interfere with ClO^- analysis. Therefore, the selective interaction of R6GH with ClO^- over other anions and metal ions suggests that R6GH

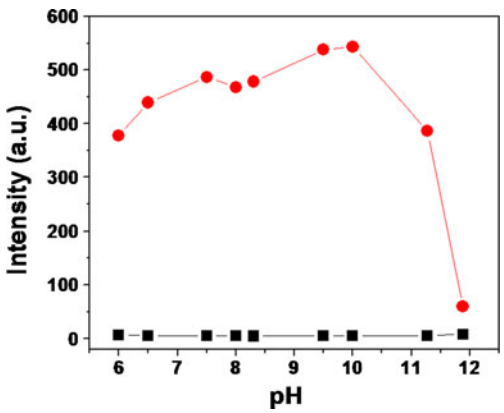
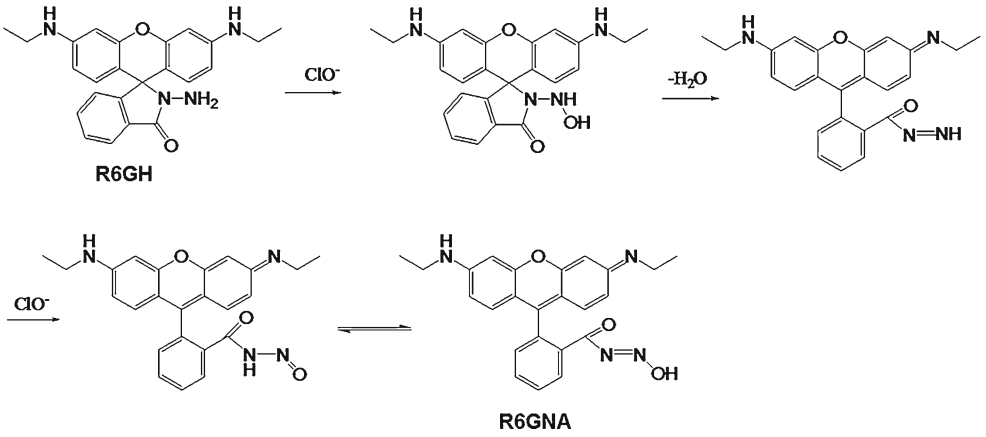


Fig. 5 pH profiles of the fluorescence intensity of R6GH (5 μM) at 548 nm in the absence and presence of ClO^- in H_2O

Scheme 2 Proposed ClO^--promoted ring opening of spirolactam of R6GH



could be used as a potential candidate for the biological imaging applications.

Next, the fluorescent titration profiles of R6GH (5 μM) with NaClO are shown in Fig. 4. The titration of ClO^- into R6GH gave a strong fluorescence enhancement with the increase of the added ClO^- concentrations. The enhancement of emission intensity in ClO^- titrations saturated at the addition of 4.0 equivalents of NaClO. From the changes in ClO^--dependent fluorescent intensity, the detection limit was estimated to be 2×10^{-8} M (for signal-to-noise ratio of 3:1) (Fig. S3, ESI). Such a low detection limits is indeed competitive with most of the fluorimetric or colorimetric sensors previously reported. In the pH range from 6.0 to 11.85, the ClO^--induced R6GH fluorescence is pH-independent and the free R6GH has no appreciable emission (Fig. 5). This property of R6GH suggests that no buffer solutions are required for the detection of the ClO^- anion, which is convenient for the practical application.

Both absorption and fluorescence data lead to a significant OFF-ON signal, indicating that the formation of the delocalized xanthane moiety of the rhodamine 6G take place. From the molecular structure and spectral results of R6GH, it is concluded that the addition of the ClO^- anion oxidized the hydrazo group to form N-OH intermediates, which initiated the ring opening of spirolactam to form a *N*-nitrosamide derivative, as depicted in Scheme 2. To elucidate the oxidized product of R6GH by ClO^-, the oxidized product was analyzed by the high-resolution mass spectra (HRMS) (Fig. S4, ESI). The mass spectra showed clear peaks (m/z) of the oxidized product of rhodamine 6G *N*-nitrosamide (R6GNA) at 415.2024.

Further experiments for ClO^--selective sensing were carried out with R6GH (5 μM) in water at pH 7.0 with an excitation at 505 nm in the presence of a wide range of the environmentally and biologically relevant metal ions and anions including sodium salts of Cl^-, ClO_4^-, NO_2^-, NO_3^- and SO_4^{2-} (100 equiv), nitrate salts of Ca^{2+}, K^+, Mg^{2+}, Pb^{2+}, Ni^{2+}, Fe^{3+}, Zn^{2+}(10 equiv), nitrate salts of Cu^{2+} and Hg^{2+} (1 equiv), TBHP and H_2O_2 (10 equiv). Upon addition of 4.0 equivalents of ClO^- anion (Fig. 6), the solution above still displays a distinctly enhanced fluorescence, indicated that R6GH shows a good selectivity and sensitivity toward ClO^- over other competitive species.

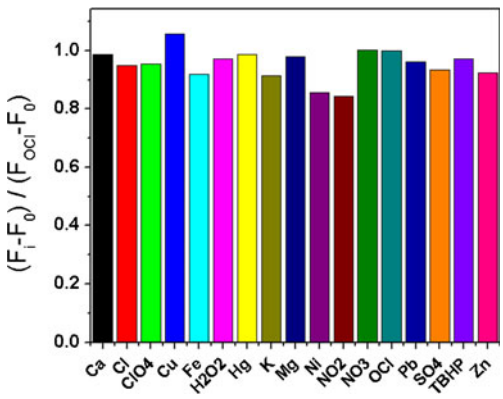


Fig. 6 Change ratio ($(F_i\text{-}F_0)/(F_{ClO^-}\text{-}F_0)$) of fluorescent intensity of R6GH upon the addition of 4.0 equivalents ClO^- in the presence of background species. Cl^-, ClO_4^-, NO_2^-, NO_3^-, SO_4^{2-} (100 equiv); Ca^{2+}, K^+, Mg^{2+}, Pb^{2+}, Ni^{2+}, Zn^{2+}(10 equiv), Fe^{3+}, Cu^{2+}, Hg^{2+} (1.0 equiv); TBHP and H_2O_2 (10 equiv) in H_2O at pH 7.0

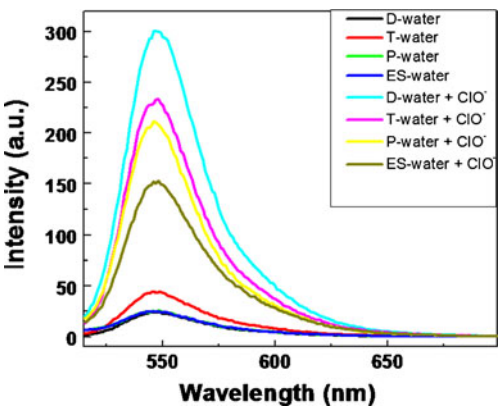


Fig. 7 Fluorescence spectra of the chemosensor R6GH (2 μM) in the absence and in those spiked with 4 equivalents of the ClO^- anions in D-water, T-water, P-water and ES-water

It is important to form a practical quality sensor to detect target analytes under environmental conditions. Such an application requires detailed studies of chemosensor performance in the environmental samples. Due to its excellent spectroscopic selective and sensitive properties, we chose natural water samples from the campus of Tianjin University of Technology (TJUT), the samples including: pool water (P-water), earth-soaked water (ES-water) and tap water (T-water). The selected water samples were analyzed with and without the addition of ClO^- (Fig. 7). At the first step, we tested the ability of the chemosensor R6GH to respond to ClO^- in the above natural water samples. In the absence of the ClO^- anions, only T-water shows a remarkable emission intensity enhancement, which means the presence of the ClO^- anions in this water sample. Next, the responses of R6GH to ClO^- in samples spiked with ClO^- were investigated. In each case, R6GH shows significant fluorescence turn-on of the emission band at 548 nm. For further considering the chemosensor can quantization detecting the ClO^- anion in natural water, ES-water samples were analyzed with and without the addition of ClO^- by fluorescence titrations. The intensity of the emission band at 548 nm increased gradually with the addition of NaClO (Fig. S5, ESI). This result indicates that R6GH can detect nanomolar scale of ClO^- quantitation in solutions with significantly more complex composition than laboratory conditions.

Conclusion

In summary, we have reported here a simple yet highly selective chemosensor R6GH for ClO^- based on the ring-opened processes of spirolactam of rhodamine 6G to turn on the fluorescence pathway. The chemosensor shows a remarkably high selectivity to discriminate between ClO^- and other ROS, such as H_2O_2, TBHP etc., and a wide range of the environmentally and biologically relevant anions and metal ions in junction with a visible colorimetric change from colorless to pink, leading to production of both "naked-eye" and fluorimetric detection of ClO^- anion. The chemosensor also shows good performance in natural water samples.

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