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A chemiluminescence sensor with signal amplification based on a self-immolative reaction for the detection of fluoride ion at low concentrations

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ABSTRACT

A sensory system incorporated with an amplification function was developed for the detection of trace-level fluoride ions. This sensory system comprises two steps: amplification and chemiluminescence. These steps were linked with chemical reactions and were induced continuously. The process from amplification to chemiluminescence was accomplished in this system using fluoride ions. The amplification is based on a self-immolative system that permits the detection of emissions even at low fluoride ion concentrations for systems in which chemiluminescence cannot be induced in the absence of fluoride ions. The optimal ratio of the chemiluminescent compound and the amplifier was calculated to achieve efficient amplification.

1. Introduction

Technology for the detection of trace-level substances is useful and has been applied in various fields. Specifically, convenient detection of specific harmful materials, such as fluoride ions, is very valuable. Fluoride ions cause diseases of the teeth and bones. For example, the U.S. Environmental Protection Agency recommends a fluoride concentration of 2.0 ppm in drinking water and has mandated an upper limit of 4.0 ppm.[1] Therefore, sensors and probes for detecting trace-level fluoride ions are needed in the food, farming, and environmental research industries.

Inductively coupled plasma mass spectrometry is generally used to detect trace-level substances. Signal amplification plays an important role in highly sensitive detection tools such as photomultipliers and secondary electron multipliers. However, these devices require electricity to operate, and they should not be moved frequently because movement affects their precision. Therefore, a chemical sensor that can detect objective substances on site would be very convenient. In particular, luminescent sensors are a clear and highly recommended method of visual detection.

Chemiluminescence is an attractive option for visual detection of trace-level fluoride ions. Chemiluminescence is induced by the decomposition of energized compounds, such as peroxides; it can be controlled using chemical reactions and by changing the reaction conditions. In addition, the induction of chemiluminescence does not require electricity or excitation light. Emission, including chemiluminescence, is generally a more sensitive detection method than absorption, reflection, and light scattering. However, at extremely low sensor concentrations, even effective emissive sensors almost fail to detect objective substances. Therefore, signal amplification via substrate recognition is necessary for these sensory systems.

Recently, in terms of amplification based on chemical reactions, much attention[2–9] has been paid to sequential disaggregative reactions, known as self-immolation. Self-immolative reactions have been applied in luminescent sensors and probes,[10–15] release and amplification of low molecular weight compounds,[16–19] and drug delivery systems.[20–23] For example, Shabat's group reported the fluorescence amplification of low-molecular weight compounds by disaggregation of dendritic compounds or polymers.[24–26] Attention has been focused on signal amplification by cyclical reactions with

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fluoride ions or hydrogen peroxide.[27–31] Phillips's group reported the amplification of chromophore concentration by cyclical reactions with fluoride ions or piperidine and the release of alcoholic compounds from acetals.[32–35] Furthermore, Huang's group[36] and Gabrielli's group[37] recently reported fluorescent probes with fluoride ion amplification functions.

Our idea was to fabricate a sensory system comprising two distinct steps. The resulting sensory system is based on a self-immolative system, as shown in Fig. 1, into which the function of amplifying fluoride ions is incorporated. The two steps are linked with chemical reactions and are induced continuously. The first step involves the recognition of trace-level fluoride ions and the amplification of fluoride ions. In this step, the amplifier recognizes trace-level fluoride ions as initiators and self-destructs to release several fresh fluoride ions. This self-destruction is caused repeatedly by the generated fluoride ions, resulting in the creation of more fluoride ions. This cyclical reaction involving self-destruction and recombination with fluoride ions leads to amplification of the fluoride ions. The second step involves the induction of chemiluminescence by the amplified fluoride ions. In this second step, the deprotection of the luminophore precursor by fluoride ions induces chemiluminescence.

In this work, as a chemiluminescence source, we applied compound **1**, which was reported previously (Scheme 1).[38–41] Compound **1** contains a phenol group protected with *tert*-butyldimethylsilyl ether and a dioxetane unit stabilized with a bulky adamantyl group. Compound **1** was deprotected by fluoride ion to induce chemiluminescence. However, the chemiluminescence of **1** is so weak that it can not be detected by the analyzer or by the naked eye at very low fluoride ion concentrations. Therefore, at sufficiently low fluoride ion concentrations, the detection of the chemiluminescence of **1** requires appropriate signal amplification. Compound **2** was prepared as the amplifier of fluoride ions in the developed sensory system. Fluoride ion amplification was achieved by disaggregation of **2**. Compound **2** was prepared from 4-cresol by protection with *tert*-butyldimethylsilyl ether as the triggering group for fluoride ions and was equipped with fluoromethyl groups at its 2- and 6-positions. The protecting group of **2** was cleaved by a fluoride ion, leading to disaggregation of **2** and the release of two fluoride ions through 1,4-elimination. The freshly released fluoride ions again reacted with **2**. When this cyclical reaction is performed N times (N: natural number), 2^N fresh fluoride ions are released. Finally, compound **2** was fully consumed and converted into an equivalent amount of fluoride ions. Using this amplified amount of fluoride ions, chemiluminescence of **1** was induced. Compounds **1** and **2** were prepared on the basis of literature reports, as shown in Schemes 2 and 3, respectively.[15,30]

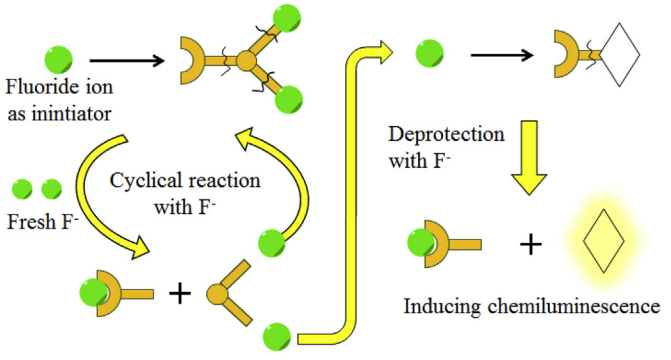
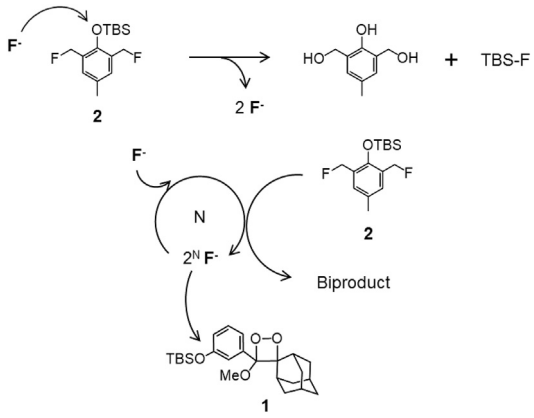
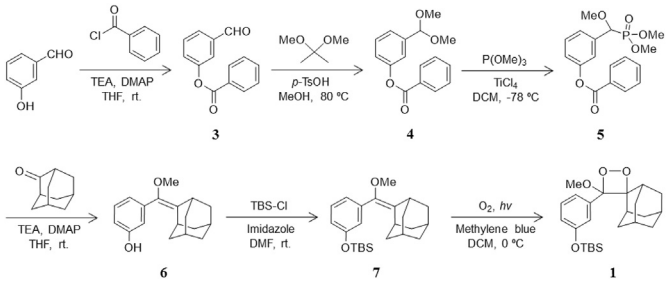


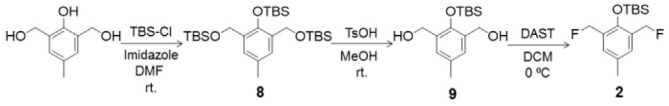
Fig. 1. Induced chemiluminescence with signal amplification of fluoride ions in the developed sensory system.



Scheme 1. Reaction sequence of amplification of the chemiluminescence **1** by **2**.



Scheme 2. Synthesis of chemiluminescent compound **1**.



Scheme 3. Synthesis of compound **2** as the amplifier of fluoride ions.

2. Results and discussion

The chemiluminescence performance of **1** was investigated to determine the lowest amount of fluoride ions required to induce chemiluminescence of **1**. Compound **1** shows blue chemiluminescence, with a peak emission at 471 nm in dichloromethane (DCM), as shown in Fig. 2a. This result is similar to a previously reported result for another solvent.[15,38–40] Time-resolved chemiluminescence spectra of **1** were measured by monitoring the luminescence intensity at the wavelength of 471 nm (Fig. 2b). It was found that the luminescence intensity depended on the amount of tetrabutylammonium fluoride (TBAF) added as a fluoride ion initiator. The addition of 2.1 mM (0.21 μmol) of TBAF to **1** caused no detectable chemiluminescence; however, the addition of 0.53 mM (0.53 μmol) of TBAF to **1** caused detectable chemiluminescence. Therefore, more than 0.53 mM of fluoride ions from the initiator or the amplifier is required to maintain constant intensity of the chemiluminescence of **1**. Conversely, inducing chemiluminescence of **1** with the amplifier **2** resulted in improved detectability of fluoride ions in the sensory system, despite the addition of less than 0.21 mM of fluoride ions from the initiator.

To investigate the self-immolative reaction of **2**, fluorine-19 nuclear magnetic resonance (^{19}F NMR) spectroscopy was conducted with the addition of various amounts of chloroform-*d* solutions of TBAF; the conversion was then calculated. Fig. 3 indicates that the self-immolative reaction of **2** completed within a short