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Discriminative sensing of sulfide and azide ions in solution by a nitrobenzoxadiazole-dansyl dyad by simply tuning the water content

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ABSTRACT

A new chromogenic and fluorogenic probe for the discriminative signaling of sulfide and azide ions using a nitrobenzoxadiazole (NBD)-dansyl dyad **3** has been investigated. Probe **3** showed prominent colorimetric and fluorescence signaling behavior toward sulfide and azide ions in aqueous tetrahydrofuran (THF). Anion selectivity was controlled by the water content in THF. In a water rich system (H_2O/THF = 99:1, v/v), probe **3** reacted mainly with sulfide ions, owing to the sulfide-selective cleavage of the NBD-OSO_2Ar bond, to yield the pink-colored NBD-SH and fluorescent dansyl acid. However, in water deficient conditions (H_2O/THF = 10:90, v/v), probe **3** exhibited both azide- and sulfide-selective reactions, due to the cleavage of the NBD-OSO_2Ar bond, to yield either NBD-N_3 (for azide ions) or NBD-SH (for sulfide ions), and dansyl acid. Azide ions can be discriminatively signaled by selective excitation at the NBD-N_3 without interference from the sulfide signaling products. This selective signaling behavior is not affected by other anions that might be present in the environmental samples. To test the practical use of this probe, we created a test strip that could be used to detect sulfide and azide ions.

1. Introduction

The development of selective and sensitive signaling systems for chemically and biologically important species is an active research field. A number of sophisticated sensors and probes exist that involve intricate signaling processes for analyte sensing [1,2]. One of the most desirable targets of sensor development is that of single molecular multianalyte signaling, where rather than the sensing of a single analyte, multiple analytes (biological or chemical) can be detected by one probe. However, it is difficult to discriminate between the subtle differences in common metal cations (e.g., Na^+ vs. K^+ and Mg^{2+} vs. Ca^{2+}) and anions (Cl^- vs. Br^-), and this makes the development of a multianalyte detection system extremely challenging [3].

Recently, a number of chemosensors that have discriminative multianalyte signaling behavior have been reported [4,5]. One example is the ratiometric fluorescence sensing of Hg^{2+} and Au^{3+} ions by an alkyne aminonaphthalimide derivative that is achieved by tuning the pH of the aqueous solutions [6]. Furthermore, the Zn^{2+}-selective dual-emission and Cu^{2+}-selective ON-OFF behavior of 1,8-naphthyridine [7], as well as the fluorescence turn-on response to Zn^{2+} and the ratiometric dual response to Al^{3+} by a quinoline-coumarin conjugate, have also been reported [8]. In addition, effective discrimination of Cu^{2+} and Hg^{2+} [9], Zn^{2+} and Cd^{2+} [10], and Ba^{2+} and Hg^{2+} using a single probe has also been reported [11].

However, most of the reported multianalyte chemosignaling systems are targeted to detect metal cations, and discriminative signaling for anions has not been significantly investigated [12]. We recently reported a nitrobenzoxadiazolyl pivalate that could selectively signal the presence of sulfide and azide ions by using different cleavage reaction pathways involving the specificity of the nucleophiles for the nitrobenzoxadiazole (NBD) moiety and pivalate, respectively [13].

The NBD moiety has been widely used as a versatile chromogenic and fluorescent labeling fluorophore for a variety of compounds having amine, thiol, and alcohol functional groups [14]. The resultant NBD derivatives have large quantum yields and long excitation and emission wavelengths that help avoid interference derived from the bio-matrix [15]. Aside from NBD, the dansyl fluorophore has also been widely used as a signaling handle for the construction of many sensors and probes. This is due to its strong fluorescence, a relatively long emission wavelength (λ_{em} = 400–600 nm), and a large Stokes shift (λ_{ex} = 330–350 nm) [16]. The dansyl moiety is generally attached to an amine group of macrocyclic polyethers, such as azacrown ethers, cyclams, and cyclens, yielding aminonaphthalenesulfonamide derivatives [16]. In addition, dansyl derivatives of amino acid residues or small

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peptide fragments, such as L-aspartic acid and dimerized L-cysteine residues, have been designed to selectively sense Hg^{2+} ions [17,18]. However, the dansyl moiety has rarely been used as a subunit for the construction of reaction-based probes [19].

Hydrogen sulfide (H_2S) is a toxic gas. However, despite its toxicity, it plays a key role in many physiological processes, including relaxation of vascular smooth muscles, mediation of neurotransmission, and inflammatory regulation [20]. Many fluorescence probes have been developed to sense and image hydrogen sulfide in biological systems [21–31]. The design of these probes is mainly based on the reduction of azide-to-amine and nitro-to-amine, a nucleophilic addition approach, or the formation of stable metal sulfide complexes. Recently, a novel approach for the signaling of H_2S by the nucleophilic substitution of NBD-based probes has been reported. The H_2S-assisted cleavage of ether, thioether, and selenoether groups of the NBD-functionalized derivatives resulted in pronounced colorimetric signaling, due to the generation of the highly chromogenic species 7-nitrobenzo-1,2,5-oxadiazole-4-thiol (NBD-SH) [32,33]. In these probes, the strong electron-withdrawing character of the nitro group makes the aromatic nitro compounds suitable for nucleophilic aromatic substitution by sulfide ions. On the other hand, NBD-coumarin and NBD-fluorescein conjugates show fluorogenic signaling behavior, in addition to colorimetric signaling [34–37]. This is attributable to the sulfide-induced generation of NBD-SH and the highly fluorescent 7-hydroxycoumarin or fluorescein. However, in spite of its wide use in various industrial processes, H_2S determination by optical chemosensors in chemical and environmental samples has not been as actively investigated.

The azide ion is also a toxic and potentially deadly species, with a lethality comparable to that of the cyanide ion. Like carbon monoxide, it binds irreversibly to the heme cofactor in hemoglobin [38]. This highly toxic species is used widely in various industrial applications, such as the preparation of biocides, detonators for explosives, laboratory preservatives, and in vehicle airbags [39]. Due to its widespread use and toxicity, the selective and sensitive determination of azide ions in chemical, environmental, and biological samples is of great practical significance. However, selective optical determination of azide ions has attracted relatively little research interest when compared with other industrially important anions, such as fluoride, cyanide, and phosphates [40,41]. Fluorescence sensors for azide ions, based on a Cu^{2+} complex of a Schiff base [42] and indolyl-naphthalene [43], have been designed. Reaction-based probes based on naphthalimide bearing an alkyne receptor for click-activated ligation with azide [44], as well as azide-selective deprotection of dichlorofluorescein chloroacetate [45] and NBD pivalate [13], have also been developed.

In this paper, we report a new single molecular multianalyte probe for two toxic and industrially relevant species of sulfide and azide ions, using an NBD-dansyl sulfonate dyad. Of note is that distinct signaling behavior of the probe toward sulfide and azide ions was achieved by simply varying the water content of the signaling medium. Although the chemical properties of the two species are quite different, we believe that the discriminative signaling of two anions by a single probe is a significant finding, and can serve as a foundation for the design of useful single molecular multianalyte signaling systems.

2. Experimental

2.1. General

4-Chloro-7-nitrobenzofurazan (NBD-Cl), dansyl chloride, sodium methoxide, sodium azide, and sodium sulfide were purchased from the Aldrich Chemical Co. All other chemicals and solvents were obtained from commercial sources, and used as received. The ^{1}H NMR (300 and 600 MHz) and ^{13}C NMR (75 and 150 MHz) spectra were measured on a Varian Gemini 2000 and Varian VNS NMR spectrometers using residual solvent signals as reference [46]. UV–vis spectra were measured with a Scinco S-3100 spectrophotometer, equipped with a Peltier temperature controller. Fluorescence spectra were obtained on a PTI QuantaMaster steady-state spectrofluorometer. Mass spectra were recorded on a Micromass Autospec mass spectrometer. Elemental analysis data was measured on a Thermo Electron corporation Flash EA 1112 analyzer. Column chromatography was carried out with silica gel (Merck, 240 mesh).

2.2. Preparation of NBD-OCH_3 (**1**) [13]

NBD-Cl (0.20 g, 1.0 mmol) was added to a solution of sodium methoxide (0.22 g, 4.0 mmol) in CH_3OH (15 mL), and the mixture was stirred for 2 h at room temperature. The resulting solution was acidified to a pH of 2 using 1 N HCl, and the precipitate that formed was filtered. The filtered solid was purified by column chromatography (silica gel, CH_2Cl_2, R_f = 0.81) to yield NBD-OCH_3 **1** (0.16 g, 84%) as a brown powder. ^{1}H NMR (300 MHz, CD_3OD) δ 8.63 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 4.21 (s, 3H). LRMS: (EI$^+$); m/z calcd for $C_7H_5N_3O_4^+$ $[M]^{+\bullet}$: 195.0, found 195.0.

2.3. Preparation of NBD-OH (**2**) [13]

NBD-OH **2** was prepared by the demethylation of NBD-OCH_3 in a solution of aqueous sodium hydroxide. NBD-OCH_3 **1** (0.20 g, 1.0 mmol) was dissolved in distilled water (100 mL). Sodium hydroxide (0.8 g, 20 mmol) was added to the solution and the mixture was refluxed for 3 h. The solution was acidified to a pH of 2 using 1 N HCl, and extracted with $(CH_3CH_2)_2O$. The organic phase was separated, evaporated, and the resulting residue was purified by column chromatography (silica gel, 1st eluent = CH_2Cl_2:CH_3OH = 5:1, v/v, R_f = 0.22; 2nd eluent = CH_3OH, R_f = 0.85) to give **2** (0.11 g, 66%) as a yellow powder. ^{1}H NMR (300 MHz, CD_3OD) δ 8.47 (d, J = 9.5 Hz, 1H), 6.05 (d, J = 9.5 Hz, 1H). LRMS: (EI$^+$); m/z calcd for $C_6H_3N_3O_4^+$ $[M]^{+\bullet}$: 181.0, found 181.0.

2.4. Preparation of NBD-dansyl dyad (**3**)

A mixture of NBD-OH **2** (0.18 g, 1.0 mmol), triethylamine (TEA) (0.28 mL, 2.0 mmol), and dansyl chloride (0.40 g, 1.5 mmol) in CH_3CN (10 mL) was stirred for 12 h at room temperature. The reaction mixture was then evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, CH_2Cl_2, R_f = 0.76) to yield the NBD-dansyl derivative **3** (0.23 g, 55%) as a dark yellow powder. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.68 (d, J = 8.6 Hz, 1H), 8.44 (d, J = 8.2 Hz, 1H), 8.43 (d, J = 8.7 Hz, 1H), 8.27 (dd, J = 7.4 and 1.2 Hz, 1H), 7.68 (dd, J = 8.6 and 7.6 Hz, 1H), 7.53 (dd, J = 8.5 and 7.4 Hz, 1H), 7.46 (d, J = 8.1 Hz, 1H), 7.26 (d, J = 7.3 Hz, 1H), 2.90 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.1, 145.8, 143.7, 143.5, 134.5, 133.6, 131.6, 131.4, 129.9, 129.9, 129.8, 129.8, 122.8, 119.0, 118.7, 116.1, 45.4. FT-IR: (ATR); 3116–2958 cm^{-1} (aromatic C—H stretch), 2875–2798 cm^{-1} (C—H stretch), 1648–1569 cm^{-1} (aromatic C=C stretch), 1542 and 1322 cm^{-1} (NO_2 stretch), 1334 and 1178 cm^{-1} (S=O stretch), 995 and 784 cm^{-1} (S—O stretch). HRMS: (FAB$^+$); m/z calcd for $C_{18}H_{14}N_4NaO_6S^+$ $[M+Na]^+$: 437.0526, found 437.0529. Anal. Calcd for $C_{18}H_{14}N_4O_6S$: C, 52.17; H, 3.41; N, 13.52. Found: C, 51.86; H, 3.72; N, 13.81.

2.5. Test strip application for sulfide and azide signaling

The test strip for the signaling of sulfide and azide ions was prepared from laboratory filter paper. Filter paper (Whatman^{TM} No.