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Hydrazine-Selective Chromogenic and Fluorogenic Probe Based on Levulinated Coumarin

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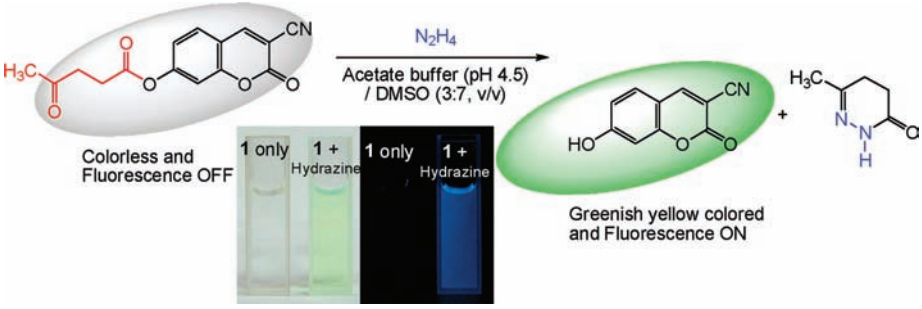
ABSTRACT



Chemosignaling of hydrazine by selective deprotection of levulinated coumarin was investigated. In the presence of hydrazine, levulinated coumarin was selectively deprotected, resulting in chromogenic and fluorescent turn-on type signaling. The selective naked-eye detectable signaling of hydrazine was possible in the presence of representative metal ions and common anions in an aqueous environment.

Hydrazine is widely used as a fuel in rocket and missile propulsion systems[1] and as a reactant in fuel cells.[2] It is a highly reactive base and a strong reducing agent and is used as an important reactant in the preparation of pharmaceuticals, pesticides, photography chemicals, emulsifiers, and dyes in various chemical industries.[3] In industry it is often applied as a chemical blowing agent and corrosion inhibitor for heating systems.[4] Hydrazine, however, is highly toxic and readily absorbed by oral, dermal, or inhalation routes of exposure. Long-term studies with laboratory animals indicate that hydrazine is mutagenic and carcinogenic.[5]

Due to its widespread applications and human toxicity, developing reliable and sensitive analytical methods for the selective detection of hydrazine is highly desirable. Hydrazine can be routinely analyzed by a wide variety of chromatographic techniques, such as gas chromatography, high performance liquid chromatography, and ion chromatography.[6] Electrochemical detection using a variety of chemically modified electrodes has also frequently been used.[7] However, there are few reports of optical analysis systems, despite their convenience. Oxidation of

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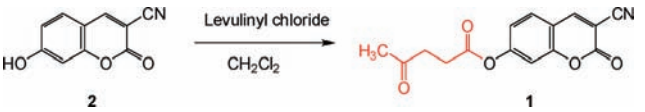
hydrazine by Tl(III) to produce fluorescent Tl(I)[8] and reaction with arenedicarboxaldehydes to produce fluorescent derivatives have been reported.[9] Fluorescence signaling with disruption of the internal hydrogen bonding by hydrazine in a carbazolopyridinophane was also reported.[10] Swager et al. reported interesting trace hydrazine detection results using a turn-on type fluorescent conjugated polymer film.[11]

Among the many sophisticated optical signaling systems, reactive chemical probes have received much interest due to their specificity and cumulative signaling effects.[12] There are many smart reactive probe systems for the analysis of metal ions, anions, and neutral molecules utilizing unique chemical transformations.[13] Particularly, deprotection of specific protecting groups has been used as a versatile signaling tool, for example the silyl ether for fluoride,[14] the boronate for hydrogen peroxide,[15] the benzenesulfonyl group for superoxide,[16] the hydrazone for Cu^{2+},[17] and the thioacetals for Hg^{2+}.[18]

Levulinoyl ester, a versatile protecting group often applied in synthetic organic chemistry,[19] can be removed selectively by treatment with hydrazine.[20] Interestingly, levulinated triphenol has been used as a hydrazine cleavable chromogenic protecting group for hydroxyl groups.[21] Recently, we reported that levulinated resorufin could be used as a selective chromogenic probe for the determination of sulfites.[22] With this background for levulinates, we devised a new hydrazine-selective signaling system. A levulinate of 3-cyano-7-hydroxycoumarin was successfully deprotected under mild conditions and acted as a selective chromogenic and fluorogenic probe for hydrazine.[23]

Levulinate **1** was prepared by the reaction of 3-cyano-7-hydroxycoumarin **2** with levulinyl chloride (65%, CH_2Cl_2) (Scheme 1).

Scheme 1. Preparation of Levulinate Probe **1**



The chromogenic signaling behavior of 3-cyano-7-hydroxycoumarin levulinate **1** was investigated in a 30% aqueous DMSO solution at pH 4.5 (acetate buffer, 10 mM). Levulinate **1** revealed moderate UV−vis absorption at 307 and 336 nm. Upon the interaction of **1** with hydrazine, a prominent absorption band centered at 426 nm developed (Figure 1). Concomitantly, a greenish yellow color, which is a characteristic of **2**, developed that allowed a colorimetric detection of hydrazine by the naked eye. The changes in absorption bands by the hydrazine-induced deprotection process were remarkable and provided ratiometric analysis for the transformation of probe **1** to **2**. With 100 equiv of hydrazine, the absorbance ratio A_{426}/A_{336} at the two characteristic wavelengths of 426 and 336 nm increased over 500-fold (from 0.014 to 7.14). Other common cations and anions were relatively nonresponsive, with A_{426}/A_{336} values varying in a limited range between 0.019 (for Pb^{2+}) and 0.078 (for Fe^{3+}) for metal ions, 0.014 (for Br^-) and 0.16 (for N_3^-) for anions, respectively (Figures S1 and S2, Supporting Information).

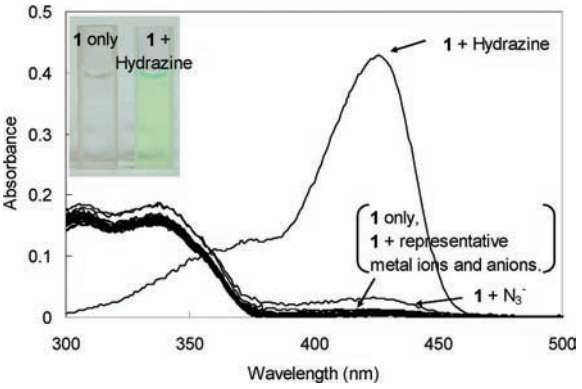


Figure 1. UV−vis spectra of probe **1** in the presence of hydrazine, representative metal ions, and anions. [**1**] = 1.0×10^{-5} M, [hydrazine] = $[M^{n+}] = [A^{n-}] = 1.0 \times 10^{-3}$ M in a mixture of acetate buffer (pH 4.5, 10 mM) and DMSO (3:7, v/v). Measured after 15 min of mixing.

The fluorogenic signaling behavior of **1** toward hydrazine was measured. Probe **1** demonstrated very weak fluorescence emission at 458 nm (Figure 2). Upon interaction with hydrazine, the fluorescence intensity at 458 nm increased 250-fold and the solution color, under illumination

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(23) We tried to apply this approach to another widely used phenolic dye resorufin. The resorufin derivative also exhibited satisfactory signaling behavior toward hydrazine; however, the interference from azide ions was significant (Figure S11, Supporting Information). On the other hand, the 7-hydroxycoumarin derivative revealed only turn-on type fluorescence signaling without any chromogenic behavior, which is inferior to the present system. Zhou, Z.; Li, N.; Tong, A. *Anal. Chim. Acta* **2011**, *702*, 82–86.

with a UV lamp, changed from colorless to bright blue. The other metal ions and anions exhibited almost no changes in emission behavior; the emission intensity ratio in the presence and absence of various ions at 458 nm, I/I_o, varied within a narrow range between 0.81 (Zn^{2+}) and 1.05 (K^+) for metal ions, 1.07 (HCO_3^-) and 2.37 (N_3^-) for anions, respectively (Figures S3 and S4, Supporting Information).

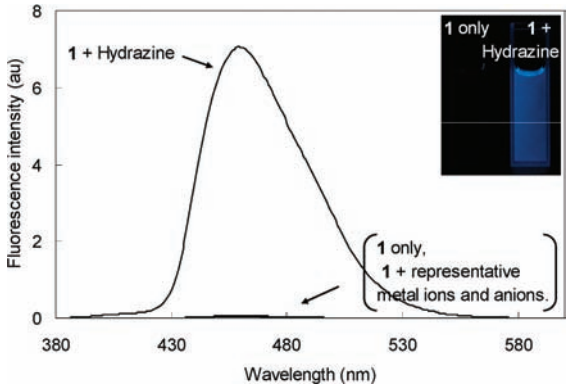
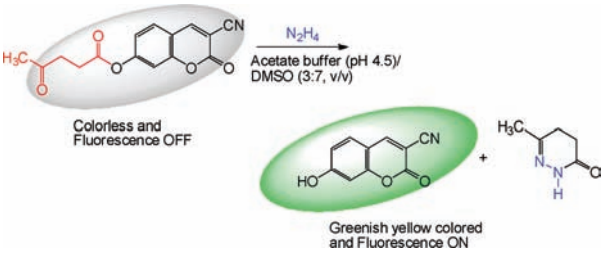


Figure 2. Fluorescence spectra of **1** in the presence of hydrazine, representative metal ions, and anions. [**1**] = 5.0×10^{-6} M, [hydrazine] = [M^{n+}] = [A^{n-}] = 5.0×10^{-4} M in a mixture of acetate buffer (pH 4.5, 10 mM) and DMSO (3:7, v/v). Measured after 15 min of mixing. λ_{ex} = 360 nm.

Signaling occurs due to the selective deprotection of the levulinate group of probe **1** by hydrazine (Scheme 2). Cleavage of the levulinate group of **1** by reaction with hydrazine is known to proceed first to the carbonyl group at the 4-position of the levulinate group and then to subsequent amide ring formation leading to cleavage of the ester function.[24] Thus generated 3-cyano-7-hydroxycoumarin exhibited its characteristic chromogenic and fluorogenic signaling behaviors.

Scheme 2. Signaling of Hydrazine by Levulinated Hydroxycoumarin **1**



The proposed hydrazine induced deprotection was evidenced by ^{1}H NMR and UV−vis measurements. By ^{1}H NMR spectroscopy, resonances for the coumarin moiety of probe **1** were observed at 8.68, 7.79, 7.23, and 7.15 ppm. However, the ^{1}H NMR spectrum of probe **1** upon treatment with 2 equiv of hydrazine was almost identical to that of 3-cyano-7-hydroxycoumarin (Figure 3). In addition, the resonances of the reaction product 4,5-dihydro-6-methylpyridazin-3(2*H*)-one was also observed (Figure S5, Supporting Information). The UV−vis spectrum of probe **1** in the presence of hydrazine was also almost identical to that of the proposed deprotection product of 3-cyano-7-hydroxycoumarin itself (Figure S6, Supporting Information).

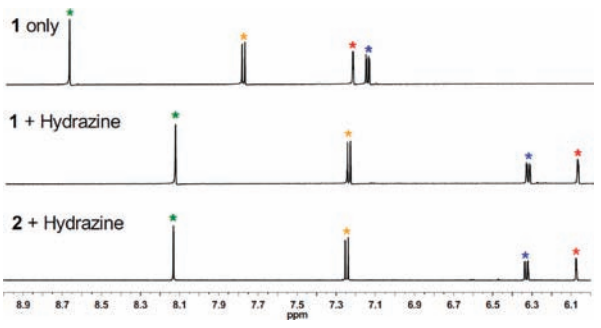


Figure 3. Partial ^{1}H NMR spectra of **1** only, **1** + hydrazine, and **2** + hydrazine. [**1**] = [**2**] = 5.0×10^{-3} M, [hydrazine] = 1.0×10^{-2} M in D_2O/DMSO-d_6 (3:7, v/v).

Competition experiments on the signaling of the **1**−hydrazine system revealed that hydrazine-induced UV−vis changes of **1** were not significantly altered in the presence of 100 equiv of coexisting common anions and metal ions except for Cu^{2+} and Hg^{2+} (Figures S7 and S8, Supporting Information). The interference from Cu^{2+} and Hg^{2+} ions was successfully circumvented by using a chelating resin Chelex-100 (Figure S9, Supporting Information). Signaling of hydrazine was finished in less than 15 min, while probe **1** showed no responses at all under the measurement conditions (Figure S10, Supporting Information).

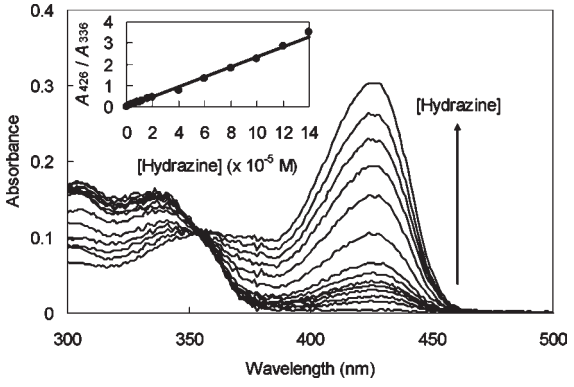


Figure 4. UV−vis titration of **1** with hydrazine. [**1**] = 1.0×10^{-5} M in a mixture of acetate buffer (pH 4.5, 10 mM) and DMSO (3:7, v/v). Measured after 15 min of each mixing.

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Finally, the quantitative analytical behavior of probe **1** for the analysis of hydrazine was investigated by UV−vis absorption titration. In spectra taken 15 min after the addition of hydrazine to **1**, the absorbance ratio (A_{426}/A_{336}) increased steadily in response to the increases in hydrazine to about 14 equiv of titration (Figure 4). From the concentration-dependent UV−vis absorption changes, the detection limit of probe **1** for the determination of hydrazine was estimated to be 2.46 μM (0.08 ppm) in a 30% aqueous DMSO solution.[25]

In summary, we have developed a new chemosignaling system for the selective sensing of hydrazine by deprotection of the levulinate group. The probe revealed a selective chromogenic and fluorogenic signaling behavior in response to hydrazine in a 30% aqueous DMSO solution. Selective signaling is based on the efficient deprotection of the levulinate group by hydrazine. The developed system could be used as a convenient signaling tool for the optical determination of hydrazine in an aqueous environment.

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Supporting Information Available. Experimental details, NMR spectra, and additional chemosignaling behavior of **1** are reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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